Chlorophenols and Their Impurities: A Health Hazard Evaluation

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Summary

Chlorinated phenols have been identified as chemicals of concern in Canada because of their toxic properties, widespread use and resulting presence in environmental media and in biota. This report is a companion issue to the Environment Canada publication *Chlorophenols and Their Impurities in the Canadian Environment* and has been prepared as a summary of published reviews and recent literature on chlorinated phenols. It concentrates on the toxicity of chlorophenols and the implications of their use for the health of Canadians. The conclusions and recommendations are based on health concerns alone, and round out the picture of the potential impact of chlorophenols on humans and their environment. The regulatory status of pentachlorophenol and related chlorophenol products is currently under review; an overview is presented in the Agriculture Canada Discussion Document on Pentachlorophenol.

Chemistry: Chlorophenols are phenols carrying one or more atoms of chlorine. Nineteen congeners are possible, exclusive of their sodium and potassium salts. Their biological activities generally increase with increasing chlorination as their solubilities decrease. Chlorophenols have readily detectable and unpleasant tastes and odours. The most widely used method of producing chlorophenols is direct chlorination of molten phenol with chlorine. Hydrolysis of polychlorinated benzenes is also used, chiefly to obtain those isomers which cannot be easily prepared by direct chlorination. At the elevated temperatures used in manufacture, various chlorinated dibenzo-p-dioxins (PCDDs), chlorinated dibenzofurans (PCDFs), chlorinated phenoxy phenols, chlorinated diphenyl ethers, and chlorinated dihydroxybiphenyls may be formed by condensation of tri-, tetra- and pentachlorophenol (PCP). In the past, PCP and tetrachlorophenol (T_4CP), the most commercially important chlorophenols in Canada, have been found to contain <100 ppm hexachlorodibenzo-p-dioxin (H_6CDD), <200 ppm heptachlorodibenzo-p-dioxin (H_7CDD) and <2000 ppm octachlorodibenzo-p-dioxin (OCDD). Currently, levels of microcontaminants are much lower, at roughly 1-10% of these early concentrations.

Quantities in Use: Manufacture of chlorophenols in Canada ceased as of July 1983. Large quantities of imported chlorophenols continue to be used. 1985 sales of chlorophenol-containing products in Canada were as follows: PCP and NaPCP, 2155 tonnes; T_4CP and NaT_4CP, 305 tonnes; 2,4,5-T_3CP and Na-2,4,5-T_3CP, <1 tonne.

Uses: Chlorinated phenols were once used in a wide range of applications, but at present most Canadian use involves PCP and T_4CP (or their alkali salts) as wood preservatives, antisapstains and mold inhibitors. The lower chlorinated phenols were used in Canada for the manufacture of higher chlorinated phenols and phenoxy herbicides; these compounds are no longer produced in this country. T_3CP is no longer registered for use in Canada.

Entry into the Environment: Most chlorophenols enter the environment at sites of use through either intentional disposal or accidental release, or as a result of commercial and domestic use of products containing these chemicals such as chlorophenol-treated wood products, pesticides, cosmetics, drugs, home care products, wood preservatives, and stains. Chlorophenols are also produced as intermediates in the degradation of such chemicals as phenoxyalkanoic acids by microorganisms and animals. Municipal chlorination of drinking water and chlorination in industrial processes can give rise to mono-, di- and trichlorophenols in the ppb range.

Environmental Fate: Chlorophenols can be degraded photolytically, and by a variety of microorganisms; hence, they are not considered to be very persistent chemicals. The higher chlorinated phenols are the slowest to degrade in soil and water, but even these usually disappear in a matter of weeks or months. In aquatic environments, the sediments act as a sink for chlorophenols, in which they may remain intact for years. PCP appears to bioconcentrate in the aquatic environment; bioconcentration factors ranging from 13 to 1000 have been reported in freshwater and marine vertebrates.

The majority of this report considers the data base available on the toxicity of chlorophenols and their impurities to laboratory mammals and to man.

Acute Toxicity: Animal studies indicate that most mono- di- and trichlorophenols are "moderately toxic" chemicals when administered orally, possessing LD_{50} values between 250 and 3000 mg/kg body weight (b.w.). T_4CP and PCP are considerably more toxic; their oral LD_{50} values are generally between 50 and 200 mg/kg b.w. PCP is more toxic to female rats than to males and more toxic to young rats than to adults. There are few published data on the health effects of acute exposure via the dermal and pulmonary exposure routes. PCP appears to be more toxic via inhalation than ingestion. Dermal exposure studies indicate that the higher chlorophenols in particular are readily absorbed through the skin. Technical PCP and T_4CP are significant skin irritants, severe eye irritants and acnegens. The acnegenic effects are the result of the microcontaminants found in commercial preparations.

Phenol and most mono-, di- and trichlorophenols are considered to be convulsive agents, while T_4CP and PCP are not. Ataxia, mental and physical fatigue, headaches, dizziness, disorientation, anorexia, nausea, vomiting, dyspnea, hyperpyrexia, tachycardia and a rise in metabolic rate are

common signs and symptoms of PCP poisoning. Most prominent are the extreme weakness, elevated body temperature and profuse sweating. Death is usually due to cardiac arrest. In man, the minimum lethal oral dose (LD_{LO}) of PCP has been estimated at 29 mg/kg body weight. With one exception, i.e., the acnegenic properties of technical T_4CP or PCP, it is generally agreed that the signs and symptoms of acute toxicity observed in animals and man exposed to chlorophenols result from the effects of the chlorophenol molecules themselves rather than from their microcontaminants.

Chlorophenols, especially T_4CP and PCP, tend to be uncouplers of oxidative phosphorylation and inhibitors of cellular ATPase, hence the profuse sweating, hyperpyrexia and weakness associated with poisoning. The precise molecular mechanisms of action are unknown.

Metabolism and Excretion: Chlorophenols appear to be excreted primarily in the urine. After exposure, small amounts accumulate in body tissues, particularly in the liver, kidney and blood. PCP can undergo a hydrolytic dechlorination to tetrachloro-p-hydroquinone and occasionally a reductive dechlorination to trichloro-p-hydroquinone. Conjugation of both PCP and tetrachloro-p-hydroquinone with glucuronides has been reported in most animals and man. The half-life of a single injected dose of PCP in human blood ranges from 30 h to 16 days, while the half-life of PCP in blood after chronic exposure is approximately 3 wk. Chlorophenols do not bioconcentrate significantly in human tissues or body fluids.

Subacute and Subchronic Toxicity: PCP has been the most widely studied chlorophenol. Purified PCP was less toxic than technical grade PCP in rat and cow feeding studies. On the basis of comparative studies, most of the toxic effects of exposure to commercial chlorophenols (most often weight loss, effects on liver, changes in clinical chemistry, and immunotoxic effects) are largely caused by microcontaminants (e.g. PCDDs, PCDFs). The parent molecule appears responsible for minor effects on body weight, liver weight, and the activity of selected liver enzymes, and perhaps immunological responses.

In man, PCP has been reported to cause painful nasal irritation at dust levels of 1-2.4 mg/m^3. The current $TLV^{(R)}$ for PCP in air is 0.5 mg/m^3. In a number of instances, fatalities have been reported as a result of extreme combined dermal and pulmonary exposures. The most commonly reported symptoms in occupationally exposed workers are dermatological, respiratory and occasionally neurological; however, a precise correlation with exposure is lacking. Signs of one or more of chloracne, neurasthesia, depression, headaches, porphyria cutanea tarda, anemia, liver and kidney functional changes have been reported in some exposed workers; on the whole these effects have not suggested severe functional impairment associated with occupational exposure.

Effects on Reproduction and Fetal Development: Chlorophenols are fetotoxic agents; however they do not appear to be teratogens. Exposure of rats to 10 mg/kg b.w. or slightly less of either purified or technical PCP has been associated with delayed fetal development, decreases in maternal weight and litter size and other fetotoxic effects. Purified PCP is more fetotoxic than the technical compound; the microcontaminants in technical PCP are known to induce liver enzymes which may then metabolize the chlorophenol more rapidly. 2,3,4,6-T_4CP and 2,4,5-T_3CP have weaker fetotoxic effects than PCP, and are not teratogenic, while 2,4,6-T_3CP is not known to adversely affect reproduction or fetal development in rats.

The effects of chlorophenols on human reproduction and fetal development have not been adequately studied.

Chronic Toxicity: Very few chronic studies of the effects of chlorophenols have been undertaken. Studies with rats have confirmed that females are more susceptible to the effects of purified PCP than males; the NOAELs in 2 year dietary exposure studies were 3 mg/kg b.w. per day and 10 mg/kg b.w. per day for females and males, respectively. At higher doses, indications of liver disorder were evident. Reversible adverse effects on the skin, kidney, the respiratory tract and the protective membrane of the eye have been frequently reported. Epidemiological studies have not adequately examined morbidity or mortality in workers chronically exposed to high levels of PCP. However, some studies (see Carcinogenicity below) have associated increased incidences of certain cancers with exposure to lower chlorophenols, most often in combination with exposure to phenoxy herbicides.

Carcinogenicity: The available data suggest that PCP is not a direct-acting animal carcinogen or tumorigen, but is a promoter. 2,4,6-T_3CP is apparently an animal carcinogen under some conditions, but not a promoter. 2-MCP, 2,4-DCP and 2,4,5-T_3CP can promote tumor formation by other tumorigenics.

There is no direct evidence that PCP or T_4CP are carcinogenic to man. There is, however, mounting evidence that workers exposed to high levels of technical grade chlorophenols and/or phenoxy herbicides have a greater risk of developing soft-tissue sarcomas and lymphomas. Case-control studies of soft-tissue sarcoma patients in Sweden and the United States indicated a several-fold relative risk (RR) for those exposed to chlorophenols, compared to those who did not appear to have been exposed. However, similar studies in New Zealand, Finland and Denmark have failed to find an association between chlorophenol exposure and various cancers. There are also anecdotal reports of an elevated frequency of lymphomas in PCP-exposed persons. An NHW-sponsored retrospective study of BC woodworkers exposed to NaPCP and NaT_4CP is currently under way.

Mutagenic and Cytogenetic Effects: Chlorophenols appear to have weak mutagenic and perhaps cytogenetic effects. PCP has not caused point mutations or chromosomal aberrations in several animal test systems, but did increase mitotic gene conversion in yeast. 2,4,6-T_3CP is a weak mutagen in both yeast and mice. Studies of PCP-exposed workers are inadequate to assess the cytogenetic effects of PCP on humans, but suggest that it can cause chromosomal abnormalities.

Toxicity of Chlorophenol Impurities: PCDDs and PCDFs are frequent microcontaminants of chlorophenols and some of their congeners have considerable toxicity. The most toxic PCDD, 2,3,7,8-T_4CDD occurs at relatively high concentrations only in 2,4,5-T_3CP. MCP and DCP are not reported to contain detectable levels of chlorinated dioxins. PCP and T_4CP contain isomers of OCDD, H_7CDD and H_6CDD, and recent analyses have detected very low concentrations of P_5CDD and T_4CDD, including 2,3,7,8-T_4CDD. The toxic effects of acute exposure of rodents to H_6CDD, the most hazardous microcontaminant of PCP and T_4CP, are deterioration of skin, weight loss, and delayed death. The LD_{50} is approximately 1 mg/kg b.w. in most laboratory mammals. H_6CDD is teratogenic and fetotoxic. Subchronic exposure leads to thymic atrophy, splenic hypertrophy and liver lesions. H_6CDD is an animal carcinogen. Little is known about H_7CDD. OCDD is not acutely toxic at 1 mg/kg b.w., and is not acnegenic or mutagenic based on animal tests. NOAELs for teratogenicity and fetotoxicity in rats are 100 and 500 µg/kg b.w. per day respectively.

Little is known about the toxicity of the other microcontaminants, including PCDFs, polychlorinated diphenyl ethers (PCDPE) or the polychlorinated phenoxyphenols (PCPPs). Chlorine atoms in the 2,3,7, and 8 position of the dioxin molecule are known to promote toxicity; similar chlorine configurations in other tetra-, penta- and hexa-chlorinated microcontaminants may also produce toxic congeners.

The hazards associated with chlorophenol exposure are related to their individual and collective toxicity, as defined in experimental studies, and the degree of exposure of persons in occupational and non-occupational settings. The hazard assessment provided in this report pertains to the use of chlorophenols (almost exclusively PCP, T_4CP, and their sodium salts) in Canada.

Occupational Exposures: There is little doubt that PCP, T_4CP, and their sodium salts are toxic materials that have caused significant discomfort for exposed workers. As the most deleterious potential short-term effects of PCP and T_4CP exposure are on the fetus, pregnant women should avoid contact with high levels of these chlorophenols in air or as solutions. Long-term exposures have not caused any substantial or statistically significant effects on male reproductive functions. However, there is evidence of neurological disorders, and of effects on some organs and on the immune system following prolonged exposure to T_3CP, T_4CP, or PCP. An elevated incidence of cancer in woodworkers exposed to PCP and T_4CP has not been investigated thoroughly.

The most hazardous microcontaminant in PCP and T_4CP is H_6CDD; however, the toxic effects of subchronic exposure to this chlorodioxin at current levels are unlikely to be expressed before significant toxicity due to PCP or T_4CP is observed. The potential hazard posed by the presence of H_6CDD in PCP rests primarily with its accumulation in human tissues, especially liver and fat. Mobilization of lipid-borne H_6CDD may pose a long-term health hazard.

The major area of occupational health concern involving the use of chlorophenols in Canada is their application as wood protectants and wood preservatives in the lumber industry. There is a clearly a need to reduce occupational exposure to PCP, T_4CP and their sodium salts, particularly at facilities for wood protection and preservation. These industries have accepted guidelines for the design and operation of such facilities; the recommendations are designed to improve industrial hygiene and reduce environmental contamination. Little is known about the toxic properties of the other chlorophenols, which are not widely used in Canada.

Non-occupational Exposure: Levels of exposure to chlorophenols in the ambient environment are poorly documented. Chlorophenol concentrations in outdoor air at large are unlikely to be above 10 ng/m^3. Indoor air of PCP-treated homes can contain 100 $\mu g/m^3$ of PCP and can cause symptoms of PCP intoxication similar to those reported by occupationally exposed persons, but most houses contain <1 $\mu g/m^3$. Exposure to chlorophenols in air is unlikely to exceed 4.3 µg/day per person. Recent suspensions of registered uses of chlorophenols in domestic spray applications and as indoor wood preservatives should be effective in reducing the potential for high indoor air levels of PCP in Canadian homes. Chlorophenol determinations in Canadian waters indicate widespread contamination, although concentrations rarely exceed 2 µg/L, the current MAC for Canadian drinking water, and most levels are much lower. Thus, total exposure in drinking water is unlikely to exceed 2.8 µg/day per person.

Canadian foods may contain low levels of PCP and T_4CP (<5 µg/kg) although certain products of the tanning industry (gelatin), some pork and poultry products (derived from animals exposed to PCP-contaminated wood, wood shavings and feed supplements) and some vegetables stored in PCP-treated wooden bins can have much higher concentrations. In Canada total chlorophenol intake in food is unlikely to exceed 6 µg/day per person. Recent restrictions on the use of chlorophenols on farms, in soil, in food containers and in the tanning industry are likely to reduce exposure of Canadians to chlorophenols in food.

Non-occupational exposures to chlorophenols from sources other than the above are difficult to quantitate but are unlikely to exceed a few µg per day. The overall health hazard associated with non-occupational exposures to chlorophenols is likely to be extremely low. A conservative estimate of the non-occupational chlorophenol daily uptake from all sources is 12.7 µg/day per adult. This level of exposure is more than 1000 times less than the lowest no-observed-effect-level reported in lab animal studies, and is not thought to pose a significant hazard to human health. However, given the limited prospects for risk management of domestic class chlorophenol-based wood preservatives, and the availability of alternative chemicals, consideration should be given to discontinuing the registration for chlorophenol-based wood preservatives for domestic applications.

Glossary of Abbreviations

Chlorophenols	
monochlorophenol	MCP
o-monochlorophenol (2-monochlorophenol)	o-MCP (2-MCP)
m-monochlorophenol (3-monochlorophenol)	m-MCP (3-MCP)
p-monochlorophenol (4-monochlorophenol)	p-MCP (4-MCP)
dichlorophenol	DCP
trichlorophenol	T_3CP
tetrachlorophenol	T_4CP
pentachlorophenol	PCP
Sodium salts of chlorophenols	
sodium trichlorophenate	Na-T_3CP
sodium tetrachlorophenate	Na-T_4CP
sodium pentachlorophenate	Na-PCP
Chlorodibenzo-p-dioxins	
monochlorodibenzo-p-dioxin	MCDD
dichlorodibenzo-p-dioxin	DCDD
trichlorodibenzo-p-dioxin	T_3CDD
tetrachlorodibenzo-p-dioxin	T_4CDD
pentachlorodibenzo-p-dioxin	P_5CDD
hexachlorodibenzo-p-dioxin	H_6CDD
heptachlorodibenzo-p-dioxin	H_7CDD
octachlorodibenzo-p-dioxin	OCDD
polychlorodibenzo-p-dioxin	PCDD
Chlorodibenzofurans	
monochlorodibenzofuran	MCDF
dichlorodibenzofuran	DCDF
trichlorodibenzofuran	T_3CDF
tetrachlorodibenzofuran	T_4CDF
pentachlorodibenzofuran	P_5CDF
hexachlorodibenzofuran	H_6CDF
heptachlorodibenzofuran	H_7CDF
octachlorodibenzofuran	OCDF
polychlorodibenzofuran	PCDF
Miscellaneous Chemicals	
ferric chloride	$FeCl_3$
aluminum chloride	$AlCl_3$
antimony chloride	$SbCl_3$
hydroxyl	OH
potassium carbonate	K_2CO_3
polychlorinated biphenyl	PCB
polychlorinated phenoxyphenol	PCPP
polychlorinated diphenyl ether	PCDPE
hexachlorobenzene	HCB
2,4,5-trichlorophe-noxy acetic acid	2,4,5-T
2,4-dichlorophe-noxy acetic acid	2,4-D
dimethylbenzanthracene	DMBA
deoxyribonucleic acid	DNA
adenosine triphosphate	ATP
adenosine diphosphate	ADP
adenosine triphosphatase	ATPase
Units of measure	
kilogram (10^3 g)	kg
gram	g
milligram (10^{-3} g)	mg
microgram (10^{-6} g)	µg
nanogram (10^{-9} g)	ng
picogram (10^{-12} g)	pg
litre	L
millilitre	mL (cc)
cubic meter	m^3
parts per million (10^{-6}) (mg/kg, mg/L, or µg/g)	ppm
parts per billion (10^{-9}) (µg/kg, or µg/L)	ppb
hour	h
week	wk
year	yr
degrees Celsius	°C

Miscellaneous terms

LD_{50}	Lethal dose for 50% of test species
LD_{LO}	Lethal dose, minimum
TD_{LO}	Toxic dose, minimum
NOAEL	No-observed-adverse-effect-level
RR	Relative Risk
$TLV^{(R)}$	Threshold Limit Value
MAC	Maximum Acceptable Concentration
IP	intraperitoneal
o, o	female, male
pKa	dissociation constant
pH	measure of acidity or alkalinity

Governmental departments and agencies

National Health and Welfare (Canada)	NHW
United States Environmental Protection Agency	USEPA
National Research Council of Canada	NRCC
National Institute for Occupational Safety and Health	NIOSH
National Cancer Institute	NCI
American Conference of Governmental and Industrial Hygienists	ACGIH

Non-governmental organizations

World Health Organization	WHO
International Agency for Research on Cancer	IARC
International Woodworkers of America	IWA

A. Introduction

Chlorinated phenols have been identified as chemicals of concern in Canada because of their widespread use, their presence in environmental media and some biota, and the toxic properties of these chemicals and their chlorinated contaminants. Pentachlorophenol (PCP) and tetrachlorophenols (T_4CP) are of primary interest because of their large-scale use and the resulting potential for environmental and occupational exposure of Canadians.

This report has been prepared as a summary of published reviews and recent literature on chlorinated phenols. It concentrates on the toxicity of chlorophenols and the implications of their use for the health of Canadians. The conclusions and recommendations are based on health concerns alone. This approach is not intended to convey that environmental aspects, i.e., impacts on organisms other than man are less important for regulatory decision making; rather, this approach reflects the large number of excellent reviews currently available on the environmental concerns surrounding chlorophenols. Special mention must be made of the report published by Environment Canada entitled *Chlorophenols and Their Impurities in the Canadian Environment* (Jones, 1981), its recent supplement (Jones, 1984), and criteria documents on chlorophenols, dioxins and furans by the National Research Council of Canada (NRCC, 1981, 1982, 1984). These reports concentrate on the Canadian situation and provide comprehensive discussion of environmental issues. Hence, this report is a companion issue to those publications and rounds out the picture of the impact of chlorophenols on humans and the environment. Because this report may be read without the DOE report, it summarizes much of the background information on chemistry, quantities produced, and disposal and environmental fate of chlorophenols. Readers requiring more detail than is provided in this report are referred to the specific references provided in the bibliography and to the large number of review articles and assessment documents.

Pentachlorophenol has been used throughout the world, and aspects of its effects on humans have been reviewed by Fielder (1982), Exon (1984), Wagner (1981), Crosby *et al.* (1981), USEPA (1980b), USEPA (1981a), Sittig (1980), IARC (1979a,1986) and Bevenue and Beckman (1967).

No reviews dedicated solely to the tetrachlorophenols are available although these chemicals have been extensively used in Canada and the USA. They are considered, however, by Ahlborg and Thunberg (1980), Kozak *et al.* (1979), NRCC (1982) and USEPA (1980a, 1981a).

The regulatory status of penta- and tetrachlorophenol products (lower chlorinated phenols are no longer registered for use in Canada) is currently under review; background and regulatory options are presented in a Discussion Document released recently by Agriculture Canada (1987).

Trichlorophenols have been reviewed briefly by the International Agency for Research on Cancer (IARC, 1979b) and are considered briefly in NRCC (1982), Ahlborg and Thunberg (1980), USEPA (1980a) and Kozak *et al.* (1979).

Dichlorophenols have been reviewed in USEPA (1980a, 1980c) and by Kozak *et al.* (1979), Exon (1984) and Krijgsheld and van der Gen (1986); however, there is little published information available.

The U.S. Environmental Protection Agency has recently reviewed the monochlorophenols (USEPA, 1980a, 1980d; Kozak *et al.*, 1979), as have Krijgsheld and van der Gen (1986); however, again there is a general paucity of published data.

The issue of microcontaminants in chlorophenols must be addressed in any assessment of the health hazards associated with chlorophenols. Of primary concern are the chlorinated dibenzo-p-dioxins and dibenzofurans. A brief account of their toxic properties is provided in this report. Extensive reviews of the chlorinated dioxins and furans have been published by the National Research Council of Canada (NRCC, 1981, 1984). Additional information on dioxins can be found in Fielder (1982), Hutzinger *et al.* (1981), and Kociba and Schwetz (1982).

A large number of abbreviations have been used in this report. In general, they are consistent with those used elsewhere (Jones, 1981; NRCC, 1982). A glossary of abbreviations and terms is provided on pages 8 and 9.

B. Chemistry

1. Physical and Chemical Properties of Chlorophenols

Chlorophenols are organic chemicals derived from phenol (1-hydroxybenzene) by substitution of one or more hydrogen atoms with chlorine. Nineteen congeners are possible (Table 1), exclusive of the sodium and potassium salts.

Table 1. Chlorophenol congeners

Homologue	Isomers
Monochlorophenols	2-monochlorophenol(o-monochlorophenol)
	3-monochlorophenol(m-monochlorophenol)
	4-monochlorophenol(p-monochlorophenol)
Dichlorophenols	2,3-dichlorophenol
	2,4-dichlorophenol
	2,5-dichlorophenol
	2,6-dichlorophenol
	3,4-dichlorophenol
	3,5-dichlorophenol
Trichlorophenols	2,3,4-trichlorophenol
	2,3,5-trichlorophenol
	2,3,6-trichlorophenol
	2,4,5-trichlorophenol
	2,4,6-trichlorophenol
	3,4,5-trichlorophenol
Tetrachlorophenols	2,3,4,5-tetrachlorophenol
	2,3,4,6-tetrachlorophenol
	2,3,5,6-tetrachlorophenol
Pentachlorophenol	2,3,4,5,6-pentachlorophenol

The physical and chemical properties of all 19 congeners of chlorophenol have been listed by Jones (1981); data for the chlorophenols which have recently been in commercial use are provided in Table 2.

Jones (1981) reports that with the exception of 2-MCP the chlorophenols are solids. Their biological activities (toxicity) and melting points generally increase with increasing chlorination, while their solubilities and pKa values decrease. There is little information available on the physical-chemical properties of the sodium chlorophenates; however, their solubilities are up to four orders of magnitude greater than those of their parent compounds.

Chlorophenols, particularly the lower ones, have readily detectable unpleasant tastes and odours (Table 2). Taste thresholds are so low that Maximum Acceptable Concentrations (MACs) of chlorophenols in drinking water are based on organoleptic criteria rather than on their toxic properties (USEPA 1980a, 1980b, 1980c, 1980d and NHW, 1980).

2. Synthesis of Chlorophenols

There are several methods by which chlorophenols can be prepared, including: direct chlorination, hydrolysis of chlorinated benzenes, conversion of diazonium salts of various chlorinated anilines, and chlorination of phenolsulphonic acids and benzenesulphonic acids followed by the removal of the sulphonic acid group (Doedens, 1963).

The most widely used commercial method is direct chlorination of molten phenol with chlorine (von Rumker *et al.*, 1974; Fig. 1). The reaction proceeds stepwise and all possible chlorophenols can be formed. Lower chlorinated phenols are prepared without catalysts, while higher chlorinated ones are catalyzed by such substances as $FeCl_3$, $AlCl_3$, or $SbCl_3$. Since the phenolic hydroxyl (OH) group is ortho-para directing, the main products of monochlorination are 2-, or 4-chlorophenol; the dichlorinated products are: 2,4- and 2,6-dichlorophenol and the higher chlorinated products are primarily 2,4,6-trichlorophenol, 2,3,4,6-tetrachlorophenol and pentachlorophenol.

Hydrolysis of polychlorinated benzenes is used chiefly to obtain those isomers which cannot be prepared easily by direct chlorination. Hydrolysis is carried out at high temperatures and under pressure, in aqueous alkaline solution. Very often methanol or ethanol is added to increase solubility, but these alcohols promote some side reactions to form methyl or ethyl ethers of chlorophenols; 2,5-DCP, 2,4,5-T_3CP, 2,3,5,6-T_4CP and PCP are prepared by this method. The process can lead to residues of hexachlorobenzene in the chlorophenol produced, and can result in the formation of PCDDs as by-products.

The alkaline hydrolysis method has been employed in Europe (Sittig, 1967), but not in the USA or Canada (von Rumker *et al.*, 1974), and so residues of hexachlorobenzene have only rarely been reported in PCP products in North America.

For the preparation of 3-MCP and 3,5-DCP the diazonium salt of chlorinated aniline is used. This method and the sulphonation process mentioned earlier are used for the preparation of meta-substituted chlorophenols (Doedens, 1963).

The chlorination of molten phenol creates other lower chlorinated phenols that do not react quantitatively with free chlorine, hence technical PCP often contains 4-12% T_4CP and traces of di-and trichlorophenols (Jones, 1981; Lanouette *et al.*, 1984), and technical T_4CP contains a substantial proportion of PCP (Kleinman *et al.*, 1986). At elevated temperatures, various chlorinated dibenzo-p-dioxins and chlorinated dibenzofurans may be formed by condensation of tri-, tetra-, and

pentachlorophenol. The formation of three hexachlorodibenzo-p-dioxin isomers is shown in Figure 2. This typical reaction requires the presence of a phenoxy radical which can react with another chlorophenol to form a phenoxyphenol. Further condensation leads to the formation of the second oxygen bridge. The analysis of chlorophenol production wastes can provide an indication of the reaction processes used and of the by-products formed (Hagenmaier and Berchtold, 1986).

sample sites. Chlorophenols in the air (usually PCP) have been collected by drawing air through an absorbent liquid for a given rate and measurement period, using absorbents such as K_2CO_3 (Gebefügi and Parlar, 1978) or ethylene glycol (Wyllie *et al.*, 1975). To ensure complete removal of chlorophenols from the air, as many as three in-line absorbers have been used (Wyllie *et al.*, 1975).

Table 2. Physical and chemical properties of chlorophenols which have been in commercial use[1]

Property	2-MCP	4-MCP	2,4-DCP	2,4,5-T_3CP	2,4,6-T_3CP	2,3,4,6-T_4CP	PCP
Molecular weight	128.56	128.56	163.00	197.45	197.45	231.98	266.34
B.P. (°C @ 760 mm)	174.9	219.8	210	Sublimes (275)	246	150[2]	309-310[2]
M.P. (°C @ 760 mm)	9.0	43.2 - 43.7	45	68 - 70.5	69.5	70	191
Dissoc. Cont. (Ka)	3.2×10^{-9}	6.6×10^{-10}	2.1×10^{-8}	3.7×10^{-8}	3.8×10^{-8}	4.2×10^{-6}	1.2×10^{-5}
pK	8.48 - 8.65	9.42 - 9.37	7.85	7.0 - 7.07	6.1 - 6.62	--	4.8 - 5.0
Density	1.2634[3]	1.2651[3]	--	--	--	--	1.978[3]
V.P. (mm @ °C)	1 @ 12.1	1 @ 49.8	1 @ 76.5	1 @ 72	1 @ 53.0	1 @ 100	5×10^{-6} @ 19 3.2×10^{-4} @ 30 40 @ 211.2
Flash Point (°C)	63.9	121.1	62	--	113.9	--	(non-flammable)
Taste threshold in H_2O[4] (ppb @ 25°C)	0.1 - 4[5]	0.1	0.3	--	--	1.0	30[6]
Odour Threshold in Air[4] (ppb @ 25°C)	2	250	2	11	1000	915(30°C)	1000-1600[4,6]
Solubility (moles/L @ 25°C, pH 5.1)	--	2.1×10^{-1}	3.8×10^{-2}	4.8×10^{-3}	2.2×10^{-3}	7.9×10^{-4}	3.6×10^{-5}
Appearance	Light amber liquid	Needle-like white to straw coloured crystal	Colourless needles or yellow solid	Colourless needles or grey flakes	Colourless crystals	Light brown mass	Dark coloured flakes or needle-like crystals

1. Principal source - Jones (1981).
2. Boiling point measured at 15 mm mercury for T_4CP and 754 mm mercury for PCP.
3. Density based on water at 4°C and chlorophenol at 20-30°C (Jones, 1981).
4. USEPA (1980a).
5. USEPA (1980d).
6. USEPA (1980b).

Further details of reactions involving chlorophenols, their precursors and microcontaminants can be found in Jones (1981) and Kozak *et al.* (1979).

3. Analytical Methodology for Chlorophenols

a) Sample Collection and Storage

Proper sampling and storage are essential for residue determination, particularly given the picogram or nanogram quantities often measured. It is therefore important to minimize contamination, and to collect representative samples. In most instances these requirements can be met simply by care in cleaning and choosing sample containers and in selecting

If samples cannot be processed for an extended length of time after collection, losses of chlorophenols through a variety of processes (Chapter D.2) can be reduced by refrigeration or freezing. APHA (1985) recommends preserving waste water samples which contain phenolics by acidification with H_3PO_4 and treatment with $CuSO_4$ prior to refrigeration. Edgerton *et al.* (1979) avoided photolytic losses by wrapping tubes containing urine samples in aluminum foil. Some researchers have carried the analysis for chlorophenols through immediately to extraction (Gee and Peel, 1974) or derivatization (Edgerton *et al.*, 1979), after which the samples were stored. Chlorination and oxidation of phenolics during determination can be prevented by addition of hydroxylamine hydrochloride and sodium hydrosulfite respectively (Chriswell *et al.*, 1975).

b) Sample Preparation and Analysis

Numerous techniques have been developed for the qualitative and quantitative analysis of chlorophenols. The earliest analytical procedures, primarily for PCP, were reviewed by Bevenue and Beckman (1967). Most were colorimetric techniques in which PCP was reacted with such compounds as nitric acid or 4-aminoantipyrine, and were neither very specific nor sensitive. They are no longer widely used, and are not discussed further here. Instead, in the following discussion, the recent analytical methodology of chlorophenols is reviewed in general terms. A more detailed outline of methods is given in NRCC (1982).

While certain 'clean' samples may be analyzed directly, most methods employ extractive and cleanup procedures to concentrate the chlorophenols from other chlorinated compounds which may interfere with the analysis. Biological tissues are often hydrolyzed with acid, alkali, or enzymes prior to extraction to free any conjugated PCP. The extraction technique used is dependent on the nature of the sample being analyzed. Most samples are acidified for extraction in order to convert chlorophenol residues to their molecular form, and extract the chlorophenols themselves rather than their ions (Bevenue and Beckman, 1967).

The actual extraction is accomplished by one or more of several methods (NRCC, 1982). Some researchers have used steam distillation to isolate chlorophenols. More often residues are extracted using either organic solvents (e.g. hexane, benzene, methylene chloride, ether) or resins (e.g. nonionic polystyrene resin). Generally simple extractions are performed by mixing, or solid samples may be chopped or blended with the solvent to facilitate extraction. Alternatively, extraction is by the more exhaustive Soxhlet method. Extraction efficiencies with the simpler, more rapid techniques may approach those obtained with Soxhlet extraction (Bruns and Currie, 1980). The relative efficiencies of various solvent systems have not been systematically examined to date.

Environmental or biological samples may contain organochlorines which can interfere with the detection of chlorophenols, and so most researchers employ additional techniques to 'clean up' samples (NRCC, 1982). Derivatization of chlorophenols, most often to methyl or acetyl derivatives, aids in separating them from interfering compounds or in reducing peak 'tailing' during gas chromatographic (GC) analysis. In particular, the aqueous acetylation of chlorophenols is useful to separate them from nonphenolic organochlorines which do not extract into the aqueous base used in this method (Jones, 1981).

In addition, column chromatography has been extensively used to 'clean up' extracts through selective adsorption of chlorophenols (NRCC, 1982). Florisil and silica gel columns have been used most often, while a few researchers have employed alumina columns or gel permeation chromatography, and increasingly ion exchange resins and high-performance liquid chromatography (HPLC) are being utilized.

Gas chromatography (GC) is the most widely used technique to determine chlorophenol concentrations in a diverse range of sample types (NRCC, 1982). A gas chromatograph, usually used with an electron capture (EC) or flame ionization (FI) detector, is rapid, specific, and capable of detecting chlorophenols in 'clean' matrices in the part-per-trillion ($1{:}10^{11}$ to $1{:}10^{12}$) range. Congeners are generally separated on a packed column combining liquid and solid phases (e.g. polar support-bonded, quartz capillary) prior to detection. The high temperature maintained in injection ports and GC columns may convert some chlorophenols to chlorinated dibenzo-p-dioxins, iso-predioxins, predioxins and dibenzofurans. Thus it may be that some early measurements of chlorophenols or their impurities are in error.

High-performance liquid chromatography has seen increasing application as a combined clean up, separation and detection system over the last decade. It eliminates the need for derivatization, and provides a high loading capacity for 'clean' matrices in conjunction with a comparable sensitivity to GC analysis (NRCC, 1982; Schönhaber *et al.*, 1982).

Other analytical techniques have shortcomings for routine residue analysis (Kozak *et al.*, 1979). Paper and thin-layer chromatography can separate compounds well, but are at best semi-quantitative. Ultraviolet and infrared spectroscopy are less sensitive than GC analysis. Negative chemical ionization, mass spectrometry, and mass fragmentography are of comparable sensitivity to GC, but are complex and expensive. These alternative techniques are generally used to confirm the identity of chlorophenols detected by GC. Chromatography with derivatives or in different solvents is also a useful confirmatory tool.

In general, the recovery from samples spiked with known amounts of chlorophenols is quite high, particularly for water and urine samples (most ≥90%). Recoveries from biological tissues, soils, and especially wood are often poorer and more variable, in spite of the harsher extraction procedures applied to these matrices. Some recoveries are overestimates; Zimmerli *et al.* (1980) found that in the absence of acid/alkaline hydrolysis, only 8% of 'endogenous' PCP was extracted from milk, although 82.5% of added PCP was recoverable.

4. Impurities in Chlorophenol Products

As a result of process chemistry, most commercial chlorophenol products contain appreciable amounts of impurities as well as products of degradation and condensation. Although they are present in very small quantities, some of these compounds are extremely toxic. Impurities include chlorodibenzo-p-dioxins and chlorinated diphenyl ethers, dibenzofurans, phenoxyphenols and dihydroxy biphenyls. Since many of these substances are considered inactive in terms of antimicrobial action, chlorophenols may be labelled as containing x% active and y% inactive ingredients.

The chlorinated dibenzo-p-dioxins of interest in PCP are the hexa-, hepta-, and octachlorodibenzo-p-dioxins. There are ten possible hexachloro isomers, two possible heptachloro isomers and one octachloro isomer. The amounts found in technical grade PCP vary considerably depending on the analytical technique used, the manufacturing method and the particular batch. (Predioxins, cyclohexadienones, and perhaps other major impurities can be converted to dioxin and dibenzofurans during analysis (Crosby *et al.*, 1981); hence, past determinations of concentrations of PCDDs and PCDFs may have been erroneously high).

Arsenault (1976) reported that PCP and T_4CP, the most commercially important chlorophenols, usually contained <100 ppm H_6CDD, <200 ppm H_7CDD and <2000 ppm OCDD in samples from the U.S. More recent information indicates either that levels may have declined or that past estimates were significantly in error. Miles *et al.* (1985) found that H_6CDD concentrations in 9 technical PCP formulations averaged 14.47 ppm, and ranged from 0.66 to 38.5 ppm. The corresponding values in 6 NaPCP samples were 8.67, 1.55 and 16.3 ppm. These figures are similar to those measured by Rappe *et al.* (1979) for European and American products (Table 3), who also determined that purified PCP and the lower chlorophenols have lower concentrations of PCDDs and PCDFs than technical PCP. Moreover, the degree of chlorination of the PCDD and PCDF microcontaminants is directly related to that of the predominant chlorophenol (Table 3). Fielder (1982) lists levels of H_6CDD isomers in Dowicide 7, a technical grade PCP product, as being between 1 and 5 ppm. In both reports, the most abundant isomer was 1,2,3,6,7,8-H_6CDD. Sodium pentachlorophenate had levels of H_6CDD isomers between 0.1 and 1.6 ppm. Dougherty (1978) quoted Dow reports that the newer 'clean' technical products contained less than 0.5 ppm of H_6CDD and from 2 to 16 ppm of OCDD, as part of an increased effort on the part of industry to eliminate these impurities from the chlorinated phenol in question. Chlorophenols are no longer manufactured in Canada (Chapter C.1). Recent residue concentrations in T_4CP/PCP mixtures representative of products in the Canadian marketplace in 1986 contained <1 to 4 ppm H_6CDD, 10 to 119 ppm H_7CDD and 5 to 330 ppm OCDD (Agriculture Canada, 1987).

It is rare to find T_4CDD in PCP samples currently marketed in Canada; to date the highly toxic 2,3,7,8-T_4CDD has been associated primarily with 2,4,5-T_3CP and chlorophenol products contaminated with 2,4,5-T_3CP. Recent analyses of European commercial chlorophenols have detected low part-per-billion concentrations of P_5CDD and T_4CDD, including 2,3,7,8-T_4CDD in samples of the 2,3,4,5-T_4CP and NaPCP, but not PCP (Hagenmaier, 1986; Hagenmaier and Brunner, 1987). Further information on the levels of dioxins and their physical and chemical properties can be found in Jones (1981).

Table 3. Levels of PCDDs and PCDFs in commercial European and American chlorophenols[1]

(ppm)	2,4,6-T_3CP	2,3,4,6-T_4CP	PCP^2	PCP
Tetra-CDDs	-	0.7	<0.1	<0.02
Penta-CDDs	<0.3	5.2	<0.1	<0.03
Hexa-CDDs	<0.5	9.6	8	10
Hepta-CDDs	<0.2	5.6	520	130
Octa-CDD	-	0.7	1380	210
Tetra-CDFs	1.5	10	<4	0.2
Penta-CDFs	17.5	10	40	0.2
Hexa-CDFs	36	60	90	13
Hepta-CDFs	4.8	60	400	70
Octa-CDF	-	10	260	55

1. From Rappe *et al.* (1979)
2. American product.

Chlorinated dibenzofurans are also commonly found in chlorophenols. There are 135 possible congeners. Like the PCDDs, production of the higher chlorinated PCDFs is favored under high temperature alkaline hydrolysis during chlorophenol synthesis. Recent concentrations of PCDFs in PCP have been reported by Jones (1981) to range between 0-40 ppm P_5CDF, 30-90 ppm H_6CDF, 80-400 ppm H_7CDF and 80-260 ppm OCDF. The major PCDF isomers found (Rappe *et al.*, 1978) were: 1,2,4,6,8-P_5CDF; 1,2,3,4,6,8-H_6CDF; 1,2,4,6,7,8-H_6CDF; 1,2,3,4,6,8,9-H_7CDF; 1,2,3,4,6,7,8-H_7CDF; and 1,2,3,4,6,7,8,9-OCDF. Similar concentrations are typical of commercial T_3CP and T_4CP products (Table 3); the predominant PCDFs in these chlorophenols tend to be lower than for PCP.

Little is known of the other microcontaminants of chlorophenols. Jones (1981) has tabulated the presence or absence of the polychlorinated diphenyl ethers (PCDPEs) in chlorophenols. The most frequently found PCDPEs are those with 5 or more chlorine atoms. Chlorinated phenoxyphenols (predioxins) are often present in pentachlorophenol, up to 1-5% by weight.

Figure 1. The chlorination of phenol to produce PCP.

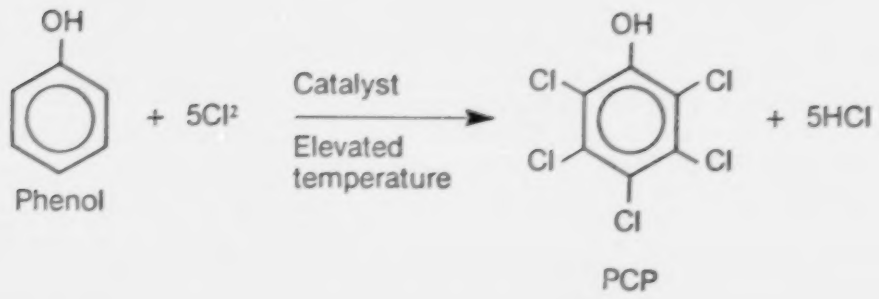
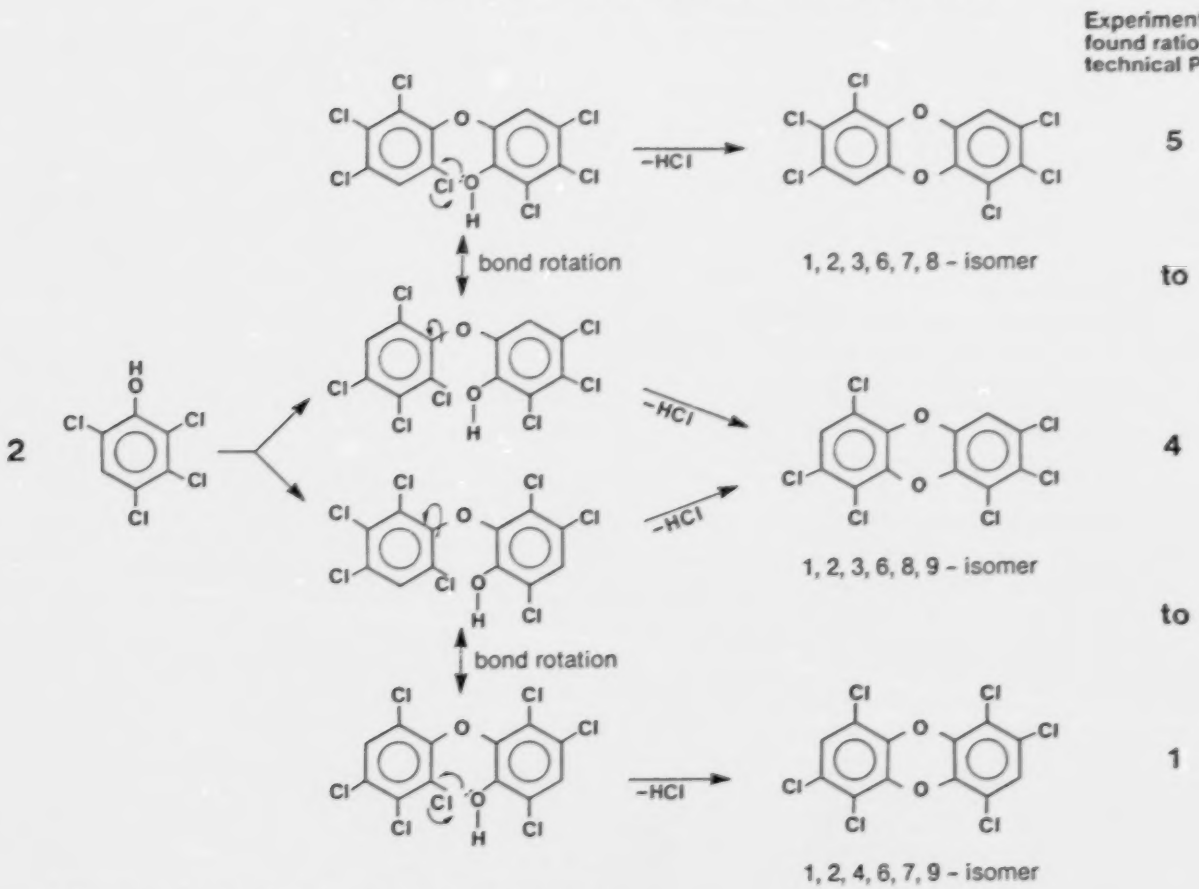


Figure 2. Typical Formation of hexachlorodibenzo-p-dioxins



From F. J. Cedar (1983) Personal Communications.
Pesticides Division, Canadian Department of Agriculture

C. Quantities, Uses and Disposal

1. Production and Importation

Chlorophenols have been produced in Canada by Dow Chemical of Canada Ltd. at Fort Saskatchewan, Alberta (2,4-DCP) and by Uniroyal Chemical Division of Uniroyal Ltd. at Clover Bar, Alberta (2,4-DCP, 2,3,4,6-T_4CP, and PCP). At one time considerable quantities were manufactured; total chlorophenol production in Canada has been estimated as 4 million kg in 1981 (Jones, 1984). Slightly more than a third each was 2,4-DCP and PCP, while most of the remaining third comprised T_4CP and its sodium salt (Jones, 1984). However, domestic production ceased as of July 1983.

Canada imports large quantities of chlorophenols, primarily from the USA and Europe. Total chlorophenol imports had declined from the early 1970's, falling below 1 million kg annually for 1979, but have exceeded 2 million kg for each of 1984 and 1985 (Statistics Canada, 1985, 1986). Sales figures compiled by Environment Canada's Commercial Chemicals Branch confirm these estimates, and indicate that PCP was the major chlorophenol imported. In 1985, sales of chlorophenol-containing products (tonnes of active ingredient) registered under the Pest Control Products Act were as follows (Environment Canada, 1986): pentachlorophenol and NaPCP, 2155 tonnes; tetrachlorophenol and NaT_4CP, 305 tonnes; 2,4,5-trichlorophenol and Na-2,4,5-T_3CP, less than 1 tonne.

The Canadian Department of Agriculture has evaluated the degree of contamination in technical tetra- and pentachlorophenols. During the early 1980's, Reichold Chemical, Inc. (Tacoma, Washington), Rhône-Poulenc (France), Vulcan Chemicals (Wichita, Kansas) and Uniroyal Chemicals (Clover Bar, Alberta) were possible suppliers of technical chlorophenols to the Canadian marketplace (Cedar, 1984). In 1987, only Vulcan Materials Co., Birmingham, Alabama and Rhône-Poulenc (France) supplied PCP to the Canadian market (Konasewich and Henning, 1988a,b).

2. Uses of Chlorophenols

In Canada, only PCP and T_4CP remain in extensive use. All trichlorophenol registrations for use under the federal Pest Control Products Act were discontinued in 1985 (Agriculture Canada, 1987). Chlorinated phenols have had very wide applications. They have been used as bactericides, molluscicides, algicides, insecticides, fungicides, mold inhibitors, antiseptics, disinfectants, as starting materials for other pesticides and also as dyes and pigments (Doedens, 1963).

Wood Treatment

The higher chlorophenols are used primarily for wood preservation. In Canada in 1981, virtually all of the PCP was used directly in commercial wood preservation (Table 4), most for pressure-treating timber for telephone poles, railway ties and outdoor construction. Lesser amounts were used to produce NaPCP, most of which was in turn used to preserve wood, and for a variety of domestic and agricultural applications, some of which also included wood treatment (e.g. paints, stains).

Substantial amounts of NaT_4CP and lesser amounts of NaPCP were used to surface-treat fresh-cut logs and lumber against sapstain fungi or mold (Table 4). Small quantities of T_3CP and NaT_3CP were once used for wood preservation in Canada, but these compounds are not in use now. Although the quantities of chlorophenols used in this manner are small compared to those of PCP used for pressure treatment, the potential for occupational exposure and environmental contamination is considerable (see Chapter F.2(a)).

Chemical Intermediates

The lower chlorophenols are used primarily as precursors in the manufacture of other chemicals. MCP, DCP and T_3CP serve as intermediates in the production of T_4CP and PCP through catalytic chlorination. Other pesticides derived from chlorinated phenols are among the most prominent of those currently in worldwide use. 2,4-DCP is used to produce the herbicides 2,4-D, 2,4-DB, 2,4-DP, Nitrofen, Genite, and Zytron, while 2,4,5-T_3CP was a building block for 2,4,5-T, Silvex, Erbon, Ronnel, and Gardona (Plimmer *et al.*, 1973). 4-MCP is used to produce the germicide 4-chlorophenol-o-cresol. Large quantities of chlorophenols at one time served as intermediates in Canada. In 1981 more than 60% of the chlorophenols used in Canada went to the production of 2,4-D alone (Jones, 1984); at present, 2,4-D is not produced in this country.

Other Applications

Reflecting their broad spectrum biocidal activity, chlorophenols are used for many other purposes, although the quantities involved are relatively small. NaPCP is used to inhibit algal and fungal growth in boiler waters, and in cooling tower waters at electrical plants. Petrochemical drilling fluids contain high concentrations of NaPCP (700-1,400 ppm) to prevent fermentation of polysaccharides, starch, and XC polymers (Jones, 1981). The sodium salts of T_4CP and PCP are added to a variety of products to inhibit microbial growth (Table 4). PCP was reportedly contained in dental care

products (Jones, 1981), bacterial soaps, laundry products, and skin medicine (Crosby *et al.*, 1981). In the domestic sector, it is used to prevent moss growth on roofs. 4-MCP was at one time contained in disinfectants for home, farm, dental, and veterinary uses, but has been largely replaced by less toxic, more cost-effective chemicals (Exon, 1984).

Table 4: Canadian use patterns of chlorophenols and their sodium salts in 1981 (Adapted from Jones, 1984)

Use	Product	Consumption[a] (kg x 10^3/yr)	% of Total
Wood preservation	PCP	1536	25.2
Wood protection	Na-PCP	32	0.5
	Na-T_4CP	786	12.9
	Na-T_3CP	1	0.02
Intermediates for phenoxy herbicides	2,4,5-T_3CP	0	0
	2,4-DCP	700	60.7
Additives[b]	NaPCP	38	0.6
	NaT_4CP	0	0
	NaT_3CP	2	0.03
TOTAL		6095	

a. Includes chlorophenols present in exports (23.8% of total consumption), principally treated wood products.
b. To adhesives, construction materials, fabrics, fibreboard products, finished paper, leather, paper machine felts, photographic solutions, pulp and paper process solutions, rayon emulsions, rubber, rubber gaskets.

The amounts of chlorophenols used in Canada, particularly in agricultural and domestic applications, may be much reduced because of 1981 restrictions on the use of some chlorophenols and their salts as pest-control products (Agriculture Canada, 1980, 1987). These product suspensions are described in Chapter F.3(a(v)).

Formulations

The parent chlorophenols are relatively insoluble in water, and hence are dissolved in other solvents for application. Fuel oil is most often used, but mineral spirits, kerosene, methylene chloride, isopropyl alcohol, or methanol have also been used. The sodium salts of chlorophenols, which are readily soluble in water, are applied as aqueous solutions. For wood preservation or protection, solutions of chlorophenols may also include one or more of alcohol (if an antifreeze additive is necessary), waxes for water-repellency (particularly for the sodium salts), co-solvents, and anti-blooming agents.

3. Waste Disposal

Since chlorophenols are no longer manufactured in Canada, CP-contaminated wastes arise principally from wood preservation sites. Disposal of wastes containing chlorophenols from pressure-treating facilities, and from sawmills using anti-sapstain solution in Canada has been described by Jones (1981). Most Canadian wood preservation plants report that they have no direct discharge. The small amounts of waste are recycled or disposed of *via* incineration or containment and evaporation. Confirmation of the adequacy of such systems of waste disposal is generally not provided.

Specific wastewater treatment techniques are used by only a few wood preserving plants. If the chlorophenol is dissolved in a carrier oil, gravity separation may be used to recover the oil and the associated chlorophenol for recycling or waste treatment. Some plants also filter out oil droplets and wood particles. Chlorophenols are effectively removed by secondary treatment under favourable conditions. Roughly 90% of total phenols were removed from waters containing wastes from phenoxy herbicide manufacture by aerated lagoon (US EPA,1971) or trickling filter/activated sludge treatments (Mills, 1959). Several laboratory and treatment plant studies have shown that PCP can be degraded by activated sludge (Dust and Thompson, 1973; Kirsch and Etzel, 1973; Etzel and Kirsch, 1974; Hickman and Novak, 1984; Bérard and Tseng, 1986), a fluidized bed reactor (Hakulinen and Salkinoja-Salonen, 1982), and a biofilm reactor (Salkinoja-Salonen *et al.*, 1984). However, of 14 municipal treatment plants surveyed by the US EPA, 8 did not remove any of the PCP load, while the remainder were considered to remove PCP (6-87%) primarily by adsorption to solids (Hickman and Novak, 1984). Further, degradation by treatment organisms is sharply reduced when chlorophenol concentrations are excessive (Broecker and Zahn, 1977; Reiner *et al.*, 1978; El-Gohary and Nasr, 1984; Salkinoja-Salonen *et al.*, 1984). If secondary treatment facilities are to remove chlorophenols reliably, they must include acclimated organisms, and ensure that chlorophenol concentrations are dilute and fairly stable (Hickman and Novak, 1984). These considerations suggest that such wastes are best handled by a facility designed specifically to treat them, rather than being treated at generalized plants.

Adsorption of chlorophenols by activated carbon is sometimes used as a final cleanup step for wastewaters; removal of 2,4-DCP (Kozak *et al.*, 1979) and PCP (Richardson, 1978) approaches 100% using this method.

Incineration has also been used to dispose of chlorophenol wastes. A controlled air incinerator destroyed greater than 99.99% of PCP in treated wood at combustion temperatures of between 910 and 1025°C, and yielded no measurable T_4CDD or T_4CDF in the offgas (Stretz and Vavruska, 1984). However, incinerator temperatures must be high enough and residence times long enough to ensure complete combustion. Crosby *et al.* (1981) report that PCP is incompletely combusted at temperatures much below 800°C; low-temperature destruction in hog-fuel or 'wigwam' burners fed chlorophenol contaminated sawdust and wood shavings can lead to the formation of chlorodibenzo-p-dioxins and furans. The degree of airborne contamination resulting from incineration processes has not been fully quantified.

Recommended waste management practices have been issued in the Canadian 'Code of Good Practice' for both the wood preservation and wood protection industries (Konasewich and Henning, 1988a,b; Konasewich *et al.*, 1983).

D. Environmental Aspects

1. Routes of Entry of Chlorophenols into the Environment

Recent estimates of chlorophenol releases to the Canadian environment have been made by Jones (1984) for 1981. These figures are several years old, but should serve to identify major sources of environmental chlorophenols.

About 5% of releases occurred at chlorophenol manufacturing sites, in wastes containing chlorophenols from incomplete reactions or recoveries, as by-products, or as a result of accidents. These releases would have included a number of chlorophenols from the manufacture of CPs and CP-derived products. The bulk of these were released as diluted effluent. Subsequent to this estimate, production of chlorophenols in Canada ceased (Chapter C.1).

Losses of chlorophenols during storage and transport were negligible.

Most (≥ 70%) of the chlorophenols released arose *in situ* from treated products. About two-thirds of this quantity came from industrial sources, most likely as leachate from treated products, as leaked drilling fluids, and spillage from in-service wood treatment. Virtually all of these chlorophenols would have been PCP, T_4CP, or their sodium salts. The remaining third of *in situ* releases were identified as 2,4-DCP from agriculture. Chlorophenols are contaminants of, and intermediates in the degradation of, such pesticides as phenoxy alkanoic acids by microorganisms (Steenson and Walker, 1957; MacRae *et al.*, 1963; Loos *et al.*, 1967a,b,c; US EPA, 1971), plants (Fawcett *et al.*, 1958; Fitzgerald *et al.*, 1967; Luckwill and Lloyd-Jones, 1960), and animals (Wright *et al.*, 1970).

The other major chlorophenol releases (22%) occurred from industries which use chlorophenols, as emissions from the incineration of wood waste at sawmills, leachate from landfills, liquid wastes from pulp mills, or discharge/spills of untreated wastes at wood preservation sites. These consisted primarily of NaT_4CP and NaPCP.

The interaction of aqueous chlorine with appropriate organic molecules will produce halogenated organic compounds including halophenols and related derivatives (Pierce, 1978a). Municipal chlorination of drinking water can give rise to mono-, di-, and trichlorophenols in the ppb range which then cause taste and odour problems. Chlorophenols may also be present in the environment because of domestic use of products such as cosmetics, drugs, home care products, wood preservatives, stains, chlorophenol- treated wood products, or pesticides which contain these chemicals. The contributions of these sources, as well as volatilization and non-point incineration, to environmental releases of chlorophenols are unknown.

2. Environmental Fate of Chlorophenols

As a result of their wide application, chlorophenols have been detected throughout the environment. Knowledge of their environmental behaviour and fate is therefore essential for effective management of chlorophenol production, use, and disposal. Mechanisms affecting environmental transport of chlorophenols include adsorption, diffusion and volatilization, leaching, surface movement, and atmospheric movement. Chlorophenols can be degraded in the environment through physico-chemical, photochemical, and microbiological action. The environmental fates of selected chlorophenols have been summarized in NRCC (1982) and Jones (1981, 1984).

a) Aquatic Systems and Aquatic Biota

Chlorophenol isomers, most commonly PCP, 2,3,4,6-T_4CP, 2,4,6-T_3CP, 2,4-DCP and 4-MCP, are commonly found in natural waters, sediments and biota (Bacon, 1978; Environment Canada, 1979; Garrett, 1980; Jones, 1981, 1984; Niimi and Cho, 1983; Fox and Joshi, 1984; Bérard and Tseng, 1986; Sithole and Williams, 1986). Residue levels in Canadian waters are for the most part low, and even in receiving waters from industrialized regions the maximum levels generally only reach several or tens of µg/L. Mg-per-litre quantities can occur immediately adjacent to discharges or spills. PCP is usually detected more frequently than other congeners.

Chlorophenol concentrations in sediments are greater than those in the overlying water, but nonetheless the maximum levels of all CP isomers in freshwater sediments of industrialized regions of Canada are usually below 50 µg/kg of dry sediment except immediately adjacent to point sources or spills.

Evaporation of chlorophenols from aquatic systems is most likely minimal. Kloppfer *et al.* (1982) determined a half-residence time for PCP in a laboratory system of 3120 h at a pH of 6.0, and detected no losses at all at pH 8.0. Some of the lower chlorophenols are moderately volatile (Table 2), but even these should evaporate only slowly under natural conditions. If the half-times for volatilization of 2-MCP and 4-MCP from 0.38 cm of still water measured by Chiou *et al.* (1980) are extrapolated to 1 m depth, the estimated half-times are 355 h and 3368 h respectively (Krijgsheld and van der Gen, 1986).

Concentrations of chlorophenols or their sodium salts in water may decrease due to photochemical degradation (Hiatt *et al.*, 1960; Wong and Crosby, 1978, 1981; Engelhardt *et al.*, 1986), metabolism by water microorganisms (Rott *et al.*, 1979; see Chapter D.2(b)), or complexation with iron, lead or copper ions (Strufe, 1968).

In waters receiving chlorophenolic wastes, invertebrates generally contain from trace levels to 20 µg/kg wet tissue of the compounds from the surrounding environment, although levels in highly contaminated environments can be an order of magnitude higher. Fishes may contain similar or slightly higher whole-body levels of chlorophenols, usually concentrated in livers and viscera; for example liver tissues from sculpins inhabiting polluted waters contained up to 1600 µg/kg wet weight of T_4CP and 2100 µg/kg of PCP, while the maximum muscle residues were 100 µg/kg and 84 µg/kg respectively (Environment Canada, 1979).

In a summary statement on the impact of PCP on a freshwater lake, Pierce (1978b) stated: "In general, the results indicate that PCP released into the aquatic ecosystem was not rapidly assimilated by photo- or microbial degradation. Acute toxicity to fish occurred by rapid uptake of the water- soluble phenate ion, whereas chronic exposure occurred by leaching of PCP from the contaminated watershed into the lake and by incorporation of PCP into the benthic food chain. Thus, once contaminated with PCP, the sediment and watershed area provided a source for chronic PCP pollution of the aquatic ecosystem". Fox and Joshi (1984) similarly identified the sediments as a sink for PCP, but in addition suggested that photolysis was an important loss process, on the basis of shifts in the ratio of T_4CP: PCP. In a more general discussion of PCP dynamics *in situ*, Crossland and Wolff (1985) concluded from their experiments in outdoor ponds and a review of the literature that photolysis rapidly removes PCP from shallow clear waters, but that it is more persistent in deep or turbid waters where other processes (sorption to sediments, biodegradation) predominate. The photolysis of PCP in aqueous solution irradiated by either ultraviolet or sunlight yields tetrachlorophenols, trichlorophenols and other related products which are themselves photochemically reactive (Hiatt *et al.*, 1960; Wong and Crosby, 1978, 1981; Engelhardt *et al.*, 1986).

b) Terrestrial Systems

Chlorophenols can enter the terrestrial system through all of the routes mentioned earlier, and can then be taken up and metabolized by microorganisms or plants, or adsorbed onto the soil. The transformations of PCP in soils have been recently reviewed by Engelhardt *et al.* (1986).

While contamination of soils by chlorophenols may be widespread, there are few reports of residue concentrations in soils, or nonexperimental terrestrial organisms. Soil residues of PCP adjacent to treated wood can be hundreds of mg/kg of dry soil (Arsenault, 1976), while levels at a Finnish sawmill were up to 70 mg/kg fresh weight of all chlorophenols (Valo *et al.*, 1984); in both instances soils outside of the immediate area contained tenths-of mg per kg quantities of CPs. Concentrations of 100 µg/kg were detected in German agricultural soil and 25-184 µg/kg dry wt. in soil from a Swiss PCP factory (WHO, 1987). Grass near the PCP factory had 67-87 µg PCP/kg dry weight, a level similar to that in grass from a reference site.

PCP degradation may proceed by both chemical and microbial means, but most degradation is presumed to be caused and promoted by microbial action. Although chlorophenols are used extensively as antimicrobial agents, they can be detoxified by certain fungi (Cserjesi and Johnson, 1972) and bacteria (Reiner *et al.*, 1978; Watanabe, 1973; Suzuki, 1977). Degradation is primarily by reductive dehalogenation to simpler tetra-, tri-, and dichlorophenols (Kaufman, 1978). As a result, the products of PCP degradation include 2,3,4,5-, 2,3,4,6-, and 2,3,5,6-T_4CP, 2,3,6-, 2,4,6-, 2,3,5-, 2,3,4-, and 2,4,5-T_3CP; the major products are 2,3,4,5-T_4CP, 2,3,6- and 2,4,6-T_3CP (Kuwatsuka, 1972; Ide *et al.*, 1972; Kuwatsuka and Igarashi, 1975). Methylation, oxidation and conjugation have also been reported (Engelhardt *et al.*, 1986). Ultimately ring cleavage occurs, and 14-CO_2 production from labelled PCP has been reported. It appears that the aromatic nuclei remain intact for long periods in phenolic compounds that contain a meta halogen (Table 5; Alexander and Aleem, 1961; Ide *et al.*, 1972; Baker and Mayfield, 1980). Consistent with this, microbiological decomposition of PCP is relatively slow (Murthy *et al.*, 1979; Suzuki and Nose, 1970; Watanabe and Hayashi, 1972). The enzyme system responsible for PCP degradation is inducible, and can enable microorganisms to degrade other chlorophenols (Engelhardt *et al.*, 1986).

Table 5. Environmental data on some chlorinated phenols[1]

Compound	Solubility g/100 g H_2O	Log_{10} Partition coefficient octanol -water	Microbial decomposition in soil suspension (days to disappear)[2] Dunkirk soil	Mardin soil
phenol	6.6	1.46[3]	2	1
2-monochlorophenol	<0.1	2.15[3]	14	47
3-monochlorophenol	0.26	2.50[3]	>72	>47
4-monochlorophenol	2.71	2.39[3]	9	3
2,4-dichlorophenol	0.45	3.06[4]	9	5
2,5-dichlorophenol	sparingly soluble	3.20[4]	>72	
2,4,5-trichlorophenol	0.12	3.72[5]	>72	>47
2,4,6-trichorophenol	0.09	3.62[4]	5	13
2,3,4,6-tetrachlorophenol	0.10	4.10[4]	>72	
pentachlorophenol	0.0014-0.0019	5.01[4]	>72	

1. From Freiter (1979)
2. Alexander and Aleem (1961)
3. Fujita *et al.* (1964)
4. Stockdale and Selwyn (1971)
5. Leo *et al.* (1971)

As a general rule, the degradation rate of PCP in soils is related to the amount of organic matter in the soil (Kuwatsuka, 1972). Degradation of PCP does not occur at all in soils that contain little organic matter (Murthy *et al.*, 1979). Pentachlorophenol may be degraded microbiologically in soil under either aerobic or anaerobic conditions (Engelhardt *et al.*, 1986). Degradation rates are a positive function of temperature (Baker *et al.*, 1980); moisture content, pH and cation exchange capacity can further influence degradation (Engelhardt *et al.*, 1986).

Plants can also take up, conjugate and metabolize PCP (Engelhardt *et al.*, 1986), but their contribution to chlorophenol dynamics is probably minimal. In tracer studies, the percentage of added PCP taken up by rice plants (Haque *et al.*, 1978; Weiss *et al.*, 1982) and aquatic macrophytes (Knowlton and Huckins, 1983) was quite low.

Adsorption to particulates can affect chlorophenol transport, particularly in soils. Acidic soils bind chlorophenols strongly, while adsorption is minimal under alkaline conditions (Choi and Aomine, 1972, 1974). Chlorophenols also adsorb to organic matter with the result that adsorption is strong in organic soils (Choi and Aomine, 1972, 1974; Schellenberg *et al.*, 1984; Seip *et al.*, 1986), and mineral soils bind relatively little of these compounds (Aly and Faust, 1964; Choi and Aomine, 1972, 1974). The higher chlorophenols, with their lower pKa and higher partition coefficients (Tables 2, 5) should be most affected by pH and organic content respectively. Studies to date have not addressed the quantitative contribution of this adsorption to chlorophenol transport under field-relevant conditions.

In instances when adsorption is minimal, it follows that leaching would be an important means of chlorophenol transport in the soil body. This is likely the case for mineral or basic soils. Reports of groundwater contamination suggest a role for leaching in chlorophenol dynamics.

c) Bioconcentration

Most research on bioaccumulation of chlorophenols has studied aquatic organisms, and indicates that bioconcentration of the compounds is moderate (Ernst and Weber, 1978; Lu *et al.*, 1978; Ernst, 1979; Veith *et al.*, 1979; Barrows *et al.*, 1980; Call *et al.*, 1980, Hattula *et al.*, 1981b; Niimi and McFadden, 1982; Virtanen and Hattula, 1982; Knowlton and Huckins, 1983; Folke *et al.*, 1984; Butte *et al.*, 1985; Paasivirta *et al.*, 1985; McKim *et al.*, 1986). Estimates of bioconcentration factors (BCFs) generally fall between 10^2 and 10^3, and are highly variable. Perhaps because of this variability, there are no obvious patterns in BCF in relation to taxonomic group of test organisms or the degree of chlorination of the chlorophenol. The range of BCFs for bacteria, algae, invertebrates, and fishes overlaps considerably. From samples of polychaetes taken from the Weser Estuary, Ernst and Weber (1978) found that the BCF of chlorophenols was inversely related to the number of chlorines on the phenol ring, but acute toxicity studies on fish (Kobayashi *et al.*, 1979; Hattula *et al.*, 1981b) suggest the opposite pattern.

The bioaccumulation study by Niimi and McFadden (1982), in which rainbow trout were exposed to field-relevant concentrations of NaPCP, is noteworthy. Trout exposed to 35 ng/L for prolonged periods concentrated it from 200 to 600 times; the amount of PCP accumulated was highest in the liver and gall bladder.

Chlorophenols clear rapidly from aquatic biota once exposure ceases, indicating that bioaccumulation *in situ* is the result of chronic exposure rather than persistence. Most half-lives for the elimination of T_3CP and PCP from a variety of aquatic organisms range from several days to several weeks (Landner *et al.*, 1977; Seppovarra and Hattula, 1977; Glickman *et al.*, 1977; Barrows *et al.*, 1980; Call *et al.*, 1980; Trujillo *et al.*, 1982; Knowlton and Huckins, 1983; Niimi and Cho, 1983; Sugiara *et al.*, 1984; Niimi and Palazzo, 1985; McKim *et al.*, 1986).

Terrestrial organisms take up PCP, and presumably other chlorophenols. However, most studies to date do not permit one to estimate the degree of bioaccumulation, because spatial heterogeneity masks the actual concentration to which organisms are exposed, and most systems studied probably have not approached steady state. Schuppener (WHO, 1987) studied PCP uptake by sterile hydroponic cultures of corn. At concentrations of up to 20 ppm, the roots accumulated as much as 151 ppm, implying a BCF of 7.55 for this structure.

The distribution and the bioconcentration potential of PCP in human tissues was studied by Geyer *et al.* (1987). Based upon daily PCP intake, PCP concentration in tissues and measured half-lives of PCP, a linear one-compartment pharmacokinetic model yielded bioconcentration factors of only 1.0 to 5.7 for five different tissues.

d) Persistence

Long-term persistence of chlorophenol isomers is only expected where input rates exceed degradative activity and/or transport out allows them to accumulate, as is illustrated by the range of residence times for chlorophenols in aquatic environments. Substantial quantities of chlorophenols are eliminated from *in situ* marine pelagic enclosures (4-MCP and 2,4-DCP --- Kuiper and Hantsveit, 1984; PCP -- Yunker, 1981, in Jones, 1984) and from freshwaters *in vitro* (2-MCP and 4-MCP --- Ettinger and Ruchhoft, 1950; 2,4-DCP -- Aly and Faust, 1964; 2,4,6-T_3CP and PCP -- Schauerte *et al.*, 1982, Sugiara *et al.*, 1984) in roughly one to three weeks. In contrast, T_4CP and PCP in sediments, where photolysis and apparently biodegradation are minimal, may persist for years or even decades (Pierce and Victor, 1978; De Laune *et al.*, 1983; Fox and Joshi, 1984).

A similar range of persistences has been reported for soils. The disappearance of at least 90% of added PCP from soils *in vitro* takes from 21 to 205 days, proceeding fastest in soils with a moderate to high organic content and acclimated microbes (Kozak *et al.*, 1979). In most instances PCP disappears in one to two months, while lower chlorophenols display similar or more rapid disappearance rates (Walker, 1954; Ide *et al.*, 1972; Kuwatsuka and Igarashi, 1975; Kozak *et al.*, 1979).

No information is available on the persistence of chlorophenols in air. Photodecomposition may be an important removal mechanism, particularly for the higher chlorophenols (Callahan *et al.*, 1979).

Since PCP is an effective wood preservative, one can infer that dissipation from treated wood is relatively slow. Nonetheless, over time substantial losses can occur. Dip- or brush-treated coniferous wood can lose 30% to 80% of PCP over a year (Morgan and Purslow, 1973; Petrowitz, 1981). Pine strips in contact with sterile and nonsterile soils lost 22% and 27% of added PCP over 50 days (Leutritz, 1965). Leaching from treated wood does not cause widespread soil contamination (Arsenault, 1976). Loss rates can be minimized by selecting an appropriate combination of wood type, moisture content, solvent, and surface sealant (Ingram *et al.*, 1981a,b, 1983; Petrowitz, 1981).

E. Toxicology

1. Introduction

The toxicology of chlorinated phenols is complicated by the presence of several toxic impurities in technical grade formulations of these products. Some of these impurities, i.e. specific congeners of the chlorinated dibenzo-p-dioxins and dibenzofurans, are extremely toxic and are found in varying concentrations in commercial chlorophenols (Chapter B.4). Thus, meaningful assessments of some reports on the toxicology of chlorophenols require an accurate knowledge of the type and degree of contamination. Extensive discussion of this issue is provided by Ahlborg and Thunberg (1980) and Kozak *et al.* (1979).

Toxicology data on both purified and commercial chlorophenols are provided in this review because both have relevance to an assessment of potential effects on health. The mode of action of chlorophenols *per se* can only be determined using purified chemicals. Furthermore, any decision to consider as "safe" any purified chlorophenols imported into Canada requires a full knowledge of the effects of the 'clean' versus the 'contaminated' product. On the other hand, toxicity studies on commercial products containing a wide variety of by-products are also useful because they provide data on the products currently in use in Canada. However, the type and degree of contamination of these products vary, and thus analysis of commercial test samples is essential if the results of toxicity studies of commercial formulations are to be compared.

2. Acute Toxicity

a) Effects on Animals

Animal studies indicate that most mono-, di- and trichlorophenols are moderately toxic chemicals when administered orally; LD_{50} values for mammalian species range between 32 and 3000 mg/kg body weight (Table 6). In general, the lower chlorinated phenols have an acute oral toxicity similar to phenol itself. T_4CP and PCP are consider-ably more toxic, the toxicity increasing with chlorination. Oral LD_{50} values are generally between 50 and 200 mg/kg body weight (Table 6). The per oral toxicity of sodium pentachlorophenate (Na-PCP) is somewhat less than that of PCP; however, it is not apparent why this difference exists (Kozak *et al.*, 1979). In addition, technical PCP is more toxic to female rats than to males (Schwetz *et al.*, 1974a) and more toxic to young rats than to adults (Schwetz *et al.*, 1978). This pattern of slightly higher toxicity in females is also apparent in subchronic and chronic studies of technical PCP and its major contaminant H_6CDD (Table 7).

There is a general paucity of published data on the effects of dermal and pulmonary exposure to chlorophenols and chlorophenates on animals. This is surprising considering the widespread use of both PCP and T_4CP and their sodium salts and the knowledge that exposures in the workplace are mainly *via* skin and lung (Fenske *et al.*, 1987). The only inhalation LC_{50} value for any chlorophenol is given in Table 6, and suggests that PCP is 4 to 7 times more toxic via inhalation than ingestion.

The effect of acute dermal exposure has been examined only in the rat and rabbit. Kozak *et al.* (1979) reported that 2-MCP, 2,3,4,6-T_4CP and PCP are readily absorbed when applied to skin. 2,4-DCP is less rapidly absorbed and 2,4,5- and 2,4,6-T_3CP do not appear to be absorbed in amounts sufficient to cause toxicity. These findings contrast with those of Huq *et al.* (1986), who found that 2-MCP, 2,4-DCP and 2,4,6-T_3CP readily passed through hairless mouse skin. Comparative studies of the oral and dermal toxicity of PCP and Na-PCP indicate that they are one-half to two-thirds as toxic to mammals when applied dermally (Table 6). Shen *et al.* (1983) found that sodium salts of 2,3,5,6-T_4CP were more toxic to rats than 2,3,5,6-T_4CP itself when applied dermally, perhaps as a result of greater absorption of some chlorophenates than chlorophenols by skin.

The variations in the LD_{50}, LD_{LO} and TD_{LO} figures reported in NRCC (1982), Jones (1981), Ahlborg and Thunberg (1980), Kozak *et al.*, (1979) and NIOSH (1983) for each animal species and route of exposure may result in part from the use of different grades of chlorophenol products or of different solvents. The type of solvent and the degree of contamination of chlorophenols tested for acute exposure is rarely described, despite the fact that the solvent vehicle can influence toxicity and that some dioxin and furan congeners are extremely toxic. In addition, acute toxic effects, other than chloracne, which are due exclusively to the presence of chlorinated dioxins or furans, are difficult to identify. Dioxins in particular have a delayed toxic effect that may be masked by the rapid onset of signs of acute exposure to the chlorophenol molecule. Furthermore, a variety of carrying solvents are used to administer chemicals for acute toxicity and some of these solvents can enhance or decrease absorption of chlorophenols, thereby affecting toxicity.

Acute doses of chlorophenols have a variety of systemic effects on test organisms (Farquharson *et al.*, 1958; Deichmann, 1943). In rats given lethal doses, MCPs, DCPs and some T_3CPs produce severe tremors and convulsions which are not observed with the higher chlorophenols. Instead, the latter

compounds are more potent uncouplers of oxidative phosphorylation, and consequently cause an elevation in body temperature. All produce muscle hypotonia, an increase in respiratory rate followed by a decrease just prior to death, and a rapid onset of rigor mortis.

In addition to its systemic effects, PCP is a significant skin irritant and a severe eye irritant (Fielder, 1982). Skin bioassay techniques indicate that technical PCP, but not purified PCP, is acnegenic and suggest that the acnegenic effects are the result of the microcontaminants found in commercial PCP, not the parent compound *per se* (Kozak *et al.*, 1979).

b) Effects on Humans

In humans, the minimum lethal oral dose (LD_{LO}) of PCP has been estimated at 29 mg/kg body weight, depending on the ambient temperature at the time of exposure, the general health of the individual and the renal competence of the victims (Kozak *et al.*, 1979). PCP is approximately five times more toxic than phenol (estimated oral LD_{LO} is 140 mg/kg). No estimates of the acute oral toxicity of other chlorophenols for humans have been published.

Numerous accidental or suicidal poisonings with commercial chlorinated phenols have been reported (Kozak *et al.*, 1979; Wood *et al.*, 1983) and nearly 60 per cent of these acute exposures have resulted in death. This literature, along with the results of animal studies, provides a relatively clear picture of the signs and symptoms in the human of acute exposure to chlorophenols. It is important to note however that no studies of the effects of pure chlorophenols on the human have been reported.

Table 6. Acute toxicity of phenol and chlorophenols for rats and mice[1]

	RAT					MOUSE			RABBIT	
	Oral	Subcut.	Dermal	IP	Inhal.	Oral	Subcut.	IP	Oral	Dermal
Phenol	530-650[2]	-	669	250	-	300	344	360	-	850
Monochlorophenol										
-2(o)	670	950	-	230	-	670	-	-	-	-
-3(m)	570	1390	-	355	-	-	-	-	-	-
-4(p)	261	1030	-	281	-	-	-	-	-	-
Dichlorophenol										
-2,4	580	1730	-	430	-	1600	-	-	-	-
-2,6	2940	1730	-	390	-	-	-	-	-	-
Trichlorophenol										
-2,3,6	-	-	-	308	-	-	-	-	-	-
-2,4,5	820[3]	2260	-	355	-	-	-	-	-	
-2,4,6	820[3]	-		276		-	-	-	-	- -
-3,4,5 -	-	-	372	-	-	-	-	-	-	-
Tetrachlorophenol										
-2,3,4,5	-	-	>2000[6]	-	-	400	-	97	-	-
-2,3,4,6	140-360[7]	210[4] -		130[8]	-	131[4]	120[5]	82-250[4,5]	-	250
-2,3,5,6	-	-	>2000[6]	-	-	109	-	48-500[4,5]	-	-
-Commercial Mix	-	-	485-565[6]	-	-	-	-	-	-	-
Tetrachlorophenate-Na	-	-	-	-	-	-	-	-	-	-
-2,3,4,5 -	-	-	>2000[6]	-	-	-	-	-	-	-
-2,3,5,6 -	-	-	294-469[6]	-	-	-	-	-	-	-
Pentachlorophenol										
-Commercial	27[4]-200[8]	100	105	56	-	74[4]	-	32[4]	70-130[5]	100-200[5]
-Pure	150-160[8]	-	-	-	-	-	-	-	-	-
Pentachlorophenate--Na	210	72	-	-	11.7[9]	-164	56	275[5]-328	100-300[5]	

1. Principle data base NIOSH (1983). LD_{50} values given as mg/kg body weight.
2. Babich and Davis (1981).
3. More recent values published by Kozak *et al.* (1979) are 4 times higher (2460-2960 mg/kg).
4. Ahlborg and Thunberg (1980).
5. Kozak *et al.* (1979).
6. Shen *et al.* (1983), commercial mixture was primarily 2,3,4,6-T_4CP.
7. Hattula *et al.* (1981a).
8. Corddry (1981).
9. Hoben *et al.* (1976).

Phenol and most mono-, di- and trichlorophenols are considered to be convulsive agents. Soon after poisoning, individuals become restless, their body temperature rises and their respiratory rate increases. After the onset of these signs, ataxia, staggering, tremors, muscle spasms and convulsions are often observed. Eventually the respiratory rate falls, dyspnea is observed and individuals become comatose and die.

Unlike the lower chlorophenols, T_4CP and PCP do not cause convulsions. Ataxia, mental and physical fatigue, headaches, dizziness, disorientation, anorexia, nausea, vomiting, dyspnea, hyperpyrexia, tachycardia and a rise in metabolic rate are common signs and symptoms of PCP poisoning. Most prominent are extreme weakness, elevated body temperature and profuse sweating. Death is due to cardiac arrest and the victims usually show a very rapid and marked rigor mortis (Ahlborg and Thunberg, 1980; Kozak *et al.*, 1979; Wood *et al.*, 1983).

The gross and histological tissue pathology associated with acute exposures to PCP is relatively consistent between laboratory animals and in humans. Oral exposures result in gastric and intestinal inflammation, the severity of which also depends on the solvent carrier and the presence of other chemicals. Pulmonary edema and congestion have been reported after oral or inhalation exposures. Splenomegaly, cardiomegaly, degenerative lesions in renal tubules, renal congestion, hepatomegaly, hepatic congestion, centrilobular degeneration and fatty degeneration in liver are also frequently observed at autopsy. Data on lower chlorinated phenols are not available.

It is generally agreed that the signs and symptoms of acute toxicity in animals and humans exposed to chlorophenols result from the effects of the chlorophenol molecule itself rather than the microcontaminants present in the technical product. This conclusion is based on the observed hyperthermia and convulsions and the rapid onset of morbidity and death associated with acute chlorophenol exposures. These signs are *not* observed in animals exposed to chlorinated dioxins or furans, and death is delayed up to three weeks in acute exposure studies with H_6CDD and T_4CDD (see Chapter E.9.a).

Treatment of poisoned individuals has had variable success. In one acute oral poisoning, gastric aspiration and lavage followed by intravenous administration of a buffered glucose solution aided recovery (Haley, 1977). The use of furosemide and mannitol to promote diuresis may also have promoted elimination of PCP and its metabolites in urine. Blood transfusions were successful in preventing the deaths of 6 of 7 infants poisoned by Na-PCP in diaper fabric (Robson *et al.*, 1969). This form of treatment is less practical for adults because of the requirement for large quantities of fresh blood. More recently Ballhorn *et al.* (1981) reported that dietary cholestyramine increases fecal excretion of PCP and its metabolites by interrupting enterohepatic circulation, which may help to reduce liver damage. Specific therapies and first aid treatment for victims of acute PCP poisoning have been discussed by Wagner (1981) and Wood *et al.* (1983).

c) Mode of Action

Chlorophenols, especially the higher ones, are uncouplers of oxidative phosphorylation (Farquharson *et al.*, 1958; Mitsuda *et al.*, 1963; Weinbach and Garbus, 1965; Carlson, 1978). At relatively high concentrations (Mitsuda *et al.*, 1963) PCP also affects the electron transport system and inhibits the formation of ATP. PCP also binds to mitochondrial ATPase (Stockdale and Selwyn, 1971), preventing energy release to the mitochondria, and catabolism increases in response to the reduced energy supply. With oxidative phosphorylation uncoupled, the increased catabolism yields higher rates of oxygen consumption, heat release, and under subchronic exposure this leads to depletion of metabolic stores, which underly respectively the elevated respiratory rate, body temperature and long-term weight loss observed in intoxicated organisms (Weinbach, 1957; Farquharson *et al.*, 1958; Mitsuda *et al.*, 1963; Wood *et al.*, 1983).

Angel and Rogers (1972) reported preliminary findings that convulsions produced by catechol, a compound structurally related to chlorophenols, were antagonized by central nicotinic blocking drugs. This observation, they suggested, would point to an effect of chlorinated phenols on the cholinergic mechanism, where a resultant increase in transmitter release produces the observed convulsions. The chlorophenate ion appears responsible for the uncoupling, while the convulsant action is caused by the undissociated molecule (Farquharson *et al.*, 1958).

Binding to enzymic protein has been reported and may lead to the observed *in vitro* inhibition of other cellular enzymes (Arrhenius *et al.*, 1977; Carlson, 1978; Kaneki and Tanaka, 1984).

3. Metabolism and Excretion

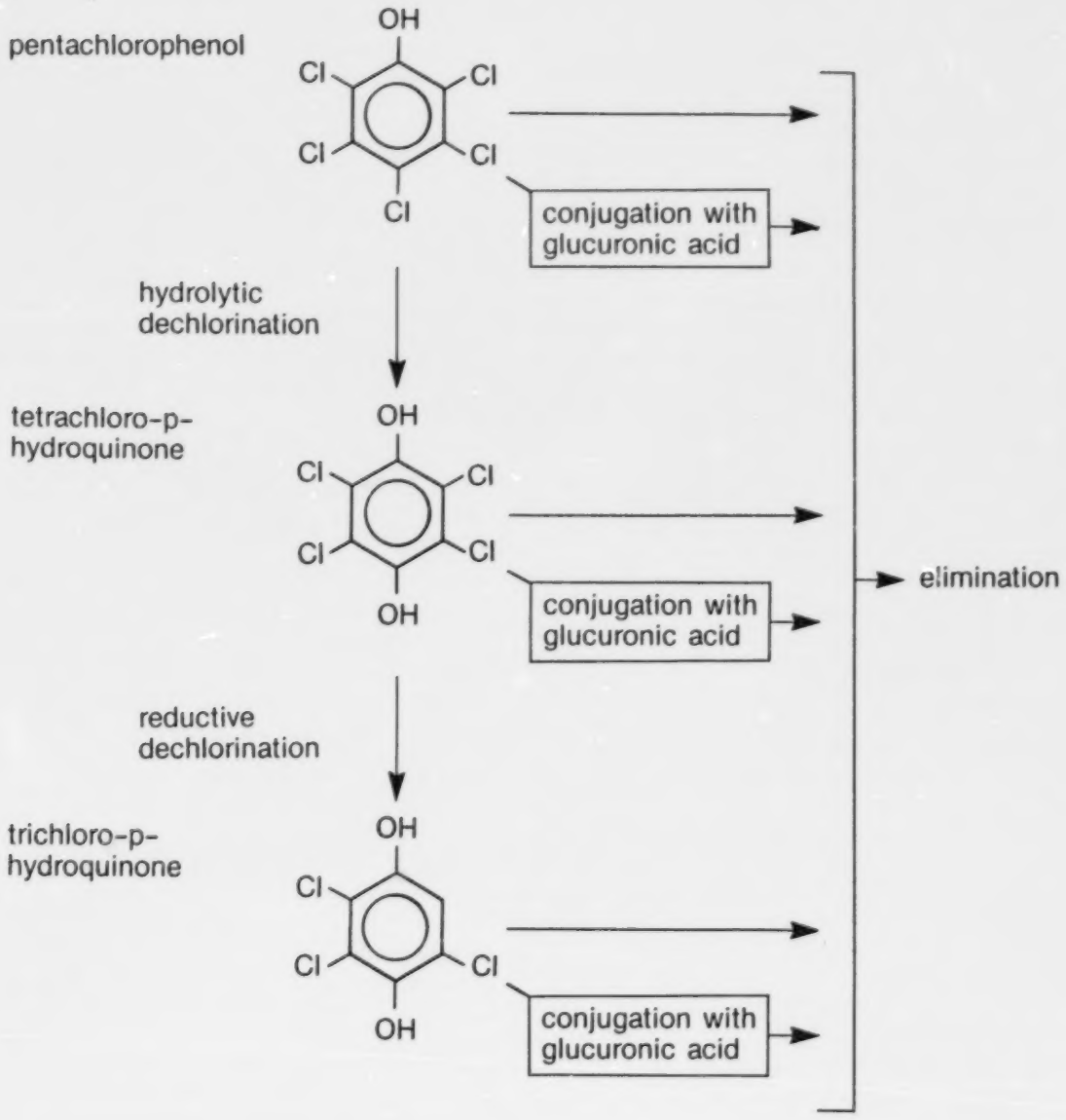
Current knowledge of the metabolism and excretion of chlorophenols comes from animal studies, cases of human poisoning and limited studies on human volunteers. Little is known about the metabolism and excretion of the lower chlorinated phenols; however, the fate of PCP has been studied in considerable detail and is reviewed by Kozak *et al.* (1979), Ahlborg and Thunberg (1980), and WHO (1987).

After experimental or accidental exposure of animals or humans to PCP, small amounts of the parent compound are found in nearly all tissues; however, concentrations in liver, brain, kidney and blood remain proportionally higher than in other tissues during the post-exposure period (Jakobson and Yllner, 1971; Larsen *et al.*, 1972; Geyer *et al.*, 1987; WHO, 1987).

The degree of metabolism and to a lesser extent the rate and route of excretion vary according to the type and amount of chlorophenol administered, the route of administration, the length of exposure, the degree of contamination of the chlorophenol and the test species used. The major compound excreted in urine in PCP injection or ingestion studies is unchanged PCP (Ahlborg *et al.*, 1974, 1978; Braun and Sauerhoff, 1976; Braun *et al.*, 1977). Lesser amounts of PCP

can undergo a hydrolytic dechlorination to tetrachloro-p-hydroquinone and occasionally a reductive dechlorination to trichloro-p-hydroquinone (Figure 3). The degree of secondary dechlorination depends on the rate at which the parent compound and the primary dechlorination product are excreted. Conjugation of both PCP and the tetrachloro-p-hydroquinone with glucuronides has been reported in most animals and man but not in the monkey (Braun and Sauerhoff, 1976; Braun *et al.*, 1977; Braun *et al.*, 1979; Uhl *et al.*, 1986). Rats and mice appear to conjugate more of the tetrachlorohydroquinone than of the PCP.

Figure 3. Metabolism of PCP[1]



In the human, oral exposure to PCP has resulted in similar proportions of the same metabolites observed in animal studies. Four male volunteers fed 0.1 mg/kg body weight of PCP (Braun *et al.*, 1978, 1979) eliminated 74% of the dose as unchanged PCP and 12% as PCP glucuronide in urine, while minor amounts of the parent compound and its conjugate were removed in the faeces. Volunteers fed PCP at higher levels by Uhl *et al.* (1986) conjugated PCP to a greater degree before excreting it after ingestion: approximately 27% of excreted PCP in urine was as glucuronide one or two days post-ingestion, and this fraction rose to a stable maximum of about 60% by thirteen days. Other studies using human volunteers have identified the excretion of tetrachlorohydroquinone and its conjugates (Ahlborg *et al.*, 1974).

Chlorophenols generally appear to be excreted rapidly from the body, and primarily in the urine. For a variety of test species and conditions, renal excretion accounts for 45% to 83% of orally administered PCP, while most of the rest is excreted via the faeces (Jakobson and Yllner, 1971; Braun and Sauerhoff, 1976; Braun *et al.*, 1977; Ballhorn *et al.*, 1981). Human volunteers studied by Braun *et al.* (1979) released 86% of ingested PCP *via* the urine within 168 h. Kozak *et al.* (1979) report that ingested PCP in humans and rats reaches maximum concentration in blood 4-6 hours after dosing, and in monkeys 12-24 h after dosing. The half-life for single doses of PCP in blood was determined as 30.2 h in the human (Braun *et al.*, 1979), 13-27 h in rats (Braun *et al.*, 1977) and 72-83 h in monkeys (Braun and Sauerhoff, 1976). Inhalation of PCP by humans also results in relatively rapid excretion in urine; half of a dose of PCP encountered over a short period of time appeared in urine within 24 h (Casarett *et al.*, 1969). Such rapid excretion may explain the low bioconcentration factors estimated by Geyer *et al.* (1987; Chapter D .4.C). Recently, Uhl *et al.* (1986) reported considerably longer half-lives for PCP elimination from human volunteers who ingested labelled PCP, of 16 ± 2.6 days from blood and 18 ± 2.4 days from urine. Ahlborg and Larsson (1978) report that in the rat, 99% of a dose of T_4CP is eliminated in the urine within 1 to 4 days, depending on the isomer. The 2,3,5,6 isomer is the most rapidly excreted and the 2,3,4,6 isomer is the slowest. 2,4,5-T_3CP and 2,4,6-T_3CP administered to rats also appear to be excreted almost completely via the urine within 24 h of dosing (Bahig *et al.*, 1981; Ahlborg and Thunberg, 1980).

Begley *et al.* (1977) reported that in chronically exposed workers the half-life of PCP in blood is close to three weeks, which is considerably longer than in most of the above studies. Similarly, Kalman and Horstman (1983) found that the half-life of 2,3,4,6-T_4CP in the blood of vacationing woodworkers was 63 hours. This rate of elimination is roughly four times slower than that determined in experiments with rats (Ahlborg and Larsson, 1978). In individuals exposed to chlorophenols for long periods of time, the circulating chlorophenols may be extensively bound to serum proteins, slowing the clearance rate of the chemicals; PCP is known to bind to plasma proteins in rats and humans. The relatively greater binding capacity of human plasma protein for PCP may explain the longer retention time of the parent compound in the human versus the rat. Recycling of parent chlorophenol in the circulatory system, kidney tubules or enterohepatic circulation via the biliary system may further prolong the excretion of small amounts of chlorophenol. It is interesting that in the workers studied by Begley *et al.* (1977) blood levels increased only slightly during a subsequent three-week period of exposure. This suggests that PCP encountered during early subsequent exposure was rapidly excreted, perhaps because it was not yet bound extensively to proteins.

Induction of liver microsomal enzymes increases the metabolism and excretion of PCP. Of special importance is the finding of Ahlborg and Thunberg (1978) that pre-treatment of rats with small amounts of 2,3,7,8-T_4CDD increased the amount of PCP metabolized to tetrachlorohydroquinone and increased the rate of excretion over the rate observed in animals not pre-treated with 2,3,7,8-T_4CDD. The net effect of the pre-treatment with dioxin was a one-third reduction in the half-life of PCP (NRCC, 1982).

Based on the undetected presence in urine of conjugates of chlorophenols and other metabolites, such as tetrachlorohydroquinone, past estimates of individual exposure to chlorophenols determined from levels in urine have probably been too low. These compounds can comprise a significant portion of the excreted chemical and must be considered carefully when estimating exposure (Currie and McDonald, 1986).

In addition, published reports of metabolism and excretion of chlorophenols by monkeys indicate that this animal is not as good a model for the human as the rat is (Braun *et al.*, 1979). Monkeys do not appear to dechlorinate PCP, nor do they excrete a single dose as rapidly as the human or the rat.

4. Subchronic Toxicity

a) Effects on Animals

Since some of the non-acute effects of exposure to technical chlorophenols are attributable to microcontaminants, it is important to consider the confounding role of these impurities in the longer-term toxicity of chlorophenols. A number of studies on rats and cows lasting between 2 and 8 months are useful in distinguishing the effects of PCP from its impurities (Table 7); these have been summarized by Fielder (1982) and NRCC (1982). On the basis of comparative studies, most of the toxic effects observed with exposure to commercial chlorophenols are apparently caused by microcontaminants. The parent molecule appears responsible primarily for minor effects on body weight, liver weight, and the induction of selected liver enzymes.

For example, rats receiving 500 mg technical PCP per kg b.w. per day for 8 months had reduced growth rates, hepatomegaly, porphyria and increased hepatic enzyme activities (aryl hydrocarbon hydroxylase, glucuronyl transferase and cytochrome P_{450}-- Goldstein *et al.*, 1977), while rats fed purified PCP under the same conditions showed only retardation of growth rate (also noted by Welsh *et al.* (1987) with subchronic exposure to 43 mg/kg b.w. per day) and an increase

in liver glucuronyl transferase activity. Rats fed 20 mg/kg b.w. per day technical PCP had elevated liver enzyme activities, while those given purified PCP did not. A similar induction of monoxygenase activity in cultured rat hepatocytes was also attributable to microcontaminants (Wollesen *et al.*, 1986).

In a similar comparative study by Johnson *et al.* (1973), 99% pure PCP and purified technical PCP (H_6CDD reduced to 1 ppm) at 10 and 30 mg/kg b.w. per day increased liver and kidney (high dose only) weights, but did not affect other variables monitored. In contrast, unpurified PCP increased liver and kidney weights, enhanced serum alkaline phosphatase activity, and decreased serum levels of erythrocytes, hemoglobin, hematocrit and albumin. These findings have been confirmed by Kimbrough and Linder (1978) and by others using different exposure routes, dosages and technical formulations (Debets *et al.*, 1980; Fleischer *et al.*, 1980; Wainstock de Calmonovici and San Martin de Viale, 1980; Knudsen *et al.*, 1974). The levels of the microcontaminants found in the technical PCP used by Goldstein *et al.* (1977) were as follows: OCDD, 1380 ppm; H_7CDD, 520 ppm; H_6CDD, 8 ppm and OCDF, 260 ppm; H_7CDF, 400 ppm; H_6CDF, 90 ppm; P_5CDF, 40 ppm and T_4 CDF, 4 ppm. Fielder (1982) concludes that, based on subchronic exposure, the no-toxic-effect-level for the rat is approximately 2 mg/kg b.w. per day when exposed to technical PCP and 200 mg/kg b.w. per day using purified PCP. Three-month exposures to technical grade PCP led to marked pathological changes in liver at 30 mg/kg and porphyria at 80 mg/kg.

Studies by the Battelle Laboratories (Peters *et al.*, 1981a,b,c) compared the effects on mice of subchronic exposure to various grades of PCP. $B6C3F_1$ mice were fed diets that led to exposures of approximately 0, 30 (low), or 75 (medium) mg PCP/kg b.w. per day of purified PCP, Dowicide EC-7, or a technical grade composite of Monsanto, Vulcan and Reichold formulations. Another group was treated at a still higher dose of each of the purified PCP, Dowicide EC-7 and composite technical grade. The higher dose was not similar for the three PCP grades administered.

Overall, the effects of these exposures were qualitatively similar, although the technical PCP often exhibited effects at a lower dose than the other two grades, which had much the same impact. The highest dose of all three grades of PCP reduced body weights or weight gain, but did not affect food or water consumption. Survival was affected only by the technical PCP, i.e., the highest concentration killed or rendered moribund all animals within 26 weeks. Dose-related liver lesions characterized by enlarged cells and nuclei, degeneration and necrosis of cells, and hyperplasia occurred with all grades, and were particularly severe in mice exposed to technical PCP. These structural changes apparently gave rise to increased liver weights and liver-to-body-weight ratios, increased activities of serum glumatic pyruvic transaminase, serum alkaline phosphatase, and liver aryl hydrocarbon hydroxylase and cytochrome P450. Concentrations of uroporphyrins and coproporphyrins were increased by all three grades of PCP, while total liver porphyrins were only increased by the EC-7 and technical compounds. Urinary bladder lesions and nasal epithelial lesions were also associated with exposure to all grades. In addition, the highest dose of technical PCP produced lesions in bone marrow, spleen, thymus, testes, and lung. Haematological parameters were affected by some PCP exposures, but not in a dose-related manner, and were not considered "biologically significant".

The subchronic toxicity of PCP has also been studied in cows (McConnell *et al.*, 1980; Kinzell *et al.*, 1981; Hughes *et al.*, 1985). These studies have confirmed that effects -- including one or more of reduced weight gain, feed consumption, anemia, reduced serum proteins, induction of mixed-function oxidases, hyperplasia of the urinary bladder, bile duct, and gall bladder, increased liver weight, decreased thymus weight, impaired kidney function and immunological changes -- were caused by microcontaminants in technical PCP administered in the feed at 10-20 mg/kg b.w. per day. Observed reductions in serum thyroxine may have been caused by the PCP itself (McConnell *et al.*, 1980); but did not occur in other studies (Hughes *et al.*, 1985). The cattle studied by McConnell *et al.* had elevated levels of octa-, hepta- and hexachlorodibenzo-p-dioxins in the liver, fat and milk after 4.5 months (Parker *et al.*, 1980).

Oral subchronic exposures to pure lower chlorinated phenols indicate that they are in turn less toxic than PCP (Table 7), but affect the same target organs. 2,4-DCP doses of up to 230 mg/kg b.w. per day (Kobayashi *et al.*, 1972), and 491 mg/kg b.w. per day (Borzelleca *et al.*, 1985) in mice, or 300 mg/L of drinking water in rats (Exon *et al.*, 1984) caused minor changes in the weight/histology of liver or spleen, but indices such as liver enzyme activities, hematological indices, and vital signs were unaffected.

More recently, Exon and Koller (1985) monitored hematological parameters and organ weights in rats exposed to lower chlorophenols in drinking water. Combined pre- and postnatal exposure to 500 mg/L of 2-MCP or 300 mg/L of 2,4-DCP significantly elevated red blood cell concentrations, hemoglobin concentrations, and packed cell volumes. Spleen and liver weights were increased significantly by exposure to 2,4-DCP and 2,4,6-T_3CP (at both 300 and 500 mg/L), but not 2-MCP. Ingestion of 2,4,6-T_3CP in amounts near the maximum tolerated dose reduced weight gains in mice (NCI, 1979; Blackburn *et al.*, 1986); mild pathological changes also occurred in the spleens (hematopoiesis) and livers (vacuolization) of rats, but not mice (NCI, 1979). No significant effects were observed in rats fed 100 mg/kg feed of 2,4,5-T_3CP, but at 300 and 1000 mg/kg dose-related, moderate pathological changes in liver and kidney, retardation of growth, and diuresis occurred (McCollister *et al.*, 1961). Hattula *et al.* (1981a) dosed rats with 0, 10, 50, and 100 mg/kg b.w. per day of 2,3,4,6-T_4CP for 55 days. Histological studies revealed severe liver injury in a small proportion of animals at the two highest doses, while other tissues were unaffected.

Subchronic studies have also been employed to investigate the immunotoxic effects of chlorophenols. Animal data on the immunotoxicity of PCP are somewhat contradictory. Cows fed

technical PCP have shown thymic hypoplasia in one study (McConnell *et al.*, 1980) but no overt differences in immunological function in another (Forsell *et al.*, 1981). Mice exposed to technical grade PCP have shown reduced humoral immunity and an *in vitro* impairment of T-cell cytolytic activity while analytical grade PCP had no effect (Kerkvliet *et al.*, 1982a, 1982b). Similarly, mice immunized against antigens and exposed to PCP *in vivo* displayed reduced humoral antibody responses to technical, but not purified PCP (Holsapple *et al.*, 1987). *In vitro* challenges of mouse spleen cell suspensions revealed that this effect was not due to the direct action of PCP on immunocompetent cells. In subchronic studies using mice, Peters *et al.* (1981a,b,c) found that none of the concentrations of pure PCP or Dowicide EC-7 used affected measures of humoral immune response, but approximately 225 mg/kg b.w. per day of pure PCP and Dowicide EC-7 enhanced splenic cell-mediated immunity. A similar dose of pure PCP resulted in a positive pokeweed mitogen response. In contrast, a lower dose of technical PCP (roughly 75 mg/kg b.w. per day) caused significant suppression of both humoral and cell-mediated immune responses. Technical grades of PCP reduced the levels of leukocytes and globulins in young pigs (Hillam and Greichus, 1983) and altered both humoral and cell-mediated immunity in rats (Exon and Koller, 1983). On the other hand, chickens fed purified PCP had depressed lymphocyte counts and humoral and lymphoproliferative responses (Prescott *et al.*, 1982). As for the lower chlorophenols, prolonged exposure to 300 mg/L of pure 2,4-DCP enhanced humoral immune responsiveness and decreased cell-mediated immunity in rats exposed both pre- and post-natally (Exon *et al.*, 1984; Exon and Koller, 1985), while 2-MCP (500 mg/L) and 2,4,6-T_3CP (300 mg/L) did not elicit a significant immune response in rats (Exon and Koller, 1983, 1985). These results suggest that both specific chlorophenols and the microcontaminants in commercial grade CPs exert an immunotoxic effect.

A neurotoxic effect of PCP (grade not specified) has been reported by Walum and Peterson (1984) based on an *in vitro* assay with cultured mice neuroblastoma cells in which an increase in cell detachments with exposure to PCP was observed. Also, a transient alteration in brain-tissue's enzyme activity was found in rats given 20 mg technical PCP per litre drinking water over a period of 3-14 weeks (Savolainen and Pekari, 1979). The significance of these findings is unclear.

b) Effects on Humans

The effects of exposure to chlorophenols have been reviewed by Fielder (1982), Kozak *et al.* (1979), Ahlborg and Thunberg (1980), and Exon (1984). Most data on the impact on humans of subacute and subchronic exposures to technical chlorophenols come from studies of occupational environments. It is difficult to assign some of the observed effects unequivocally to exposure to commercial chlorophenols, as many studies have been anecdotal, incomplete, unsuitably controlled, or confounded by alcohol consumption, tobacco smoking, or exposure to other chemicals.

Workers may display a variety of overt symptoms of chlorophenol exposure. Persons often complain of irritations of the skin, mucous membranes and respiratory tract as a result of direct or airborne contact (Gurova, 1964; May, 1973; Klemmer *et al.*, 1980; Sterling *et al.*, 1982; Embree *et al.*, 1984; Kleinman *et al.*, 1986). For example, PCP-exposed workers have reported painful nasal irritation at dust levels of 1-2.4 mg/m^3; those accustomed to exposure often tolerate levels near the upper level of this range (Deichmann and Keplinger, 1981).

Gas-mask testers exposed to trichlorophenol exhibited reduced forced expired flow and increased closing volume in their lungs relative to controls (Alexandersson and Hedenstierna, 1982). The authors observed increases in elastic recoil of the lungs and interstitial density in chest X-rays of two of the gas-mask testers and suggested that over time this exposure could lead to pulmonary dysfunction and fibrosis of the lung. Notwithstanding this suggestion, one of the two subjects returned to normal after exposure to T_3CP was discontinued.

Chronic skin ailments, particularly chloracne (but also other lesions, ulcerations and porphyria cutanea tarda) from occupational exposure to PCP or NaPCP have been reported from manufacturing and wood-preservation sites from around the world (Baader and Bauer, 1951; Behrbohm, 1959; Shirakawa *et al.*, 1959; Vinogradova *et al.*, 1973; Kozak *et al.*, 1979; Fielder, 1982; Wood *et al.*, 1983). Workers exposed to NaT_4CP (Behrbohm, 1959) and 2,4,5-T_3CP (Behrbohm, 1959; Kleu and Goltz, 1971; Goldmann, 1972; May, 1973; Jirasek *et al.*, 1974; Cook *et al.*, 1980) have also developed chloracne.

A number of data indicate that very high levels of chlorophenols may alter liver structure and function in exposed persons. Elevated levels of CPs (mostly PCP, 2,4,5-T_3CP, or their sodium salts) in occupational settings and/or as a result of industrial accidents produce symptoms of hepatotoxicity, including liver enlargement and fibrosis, elevated serum levels of liver enzymes, reduced ability to synthesize protein, or increased concentrations of liver metabolites in urine (Goldmann, 1972; May, 1973; Vinogradova *et al.*, 1973; Jirasek *et al.*, 1974; Zober *et al.*, 1981; Favaretti *et al.*, 1982; Giambelluca *et al.*, 1982; Sterling *et al.*, 1982; Fielder, 1982). However, on the whole, the findings do not suggest severe functional impairment at ambient occupational exposures. Elevations in hepatic enzymes are usually transitory and some studies have failed to find clinically significant effects of PCP exposure on serum enzyme levels (Klemmer *et al.*, 1980; Zober *et al.*, 1981, in Fielder, 1982). Further, studies which have found evidence of liver damage in exposed persons have been confounded by patterns in alcohol consumption, small sample sizes, and contradictory patterns in different enzymes (Fielder, 1982).

Begley *et al.* (1977) reported that Hawaiians working with PCP wood preservatives exhibited abnormal renal function, indicated by significantly depressed creatinine clearance.

Some workers exposed to chlorophenols report such psychological or neurological symptoms as recurring fatigue, headaches, memory loss, difficulty concentrating, sleeplessness, depression, excitability, irritability, reduced libido,

dizziness, nausea, vomiting, and neuralgia of the extremities (Baader and Bauer, 1951; Gurova, 1964; Kleu and Goltz, 1971; May, 1973; Vinogradova *et al.*, 1973; Jirasek *et al.*, 1974; Sterling *et al.*, 1982; Kleinman *et al.*, 1986). These disorders are confirmed in some instances by more objective measures. Exposure of workers to T_3CP and T_4CDD at the Seveso plant was associated with slowed visual reaction times, and increased proportions of theta brain waves (Gilioli *et al.*, 1983), while sensory nerve conduction velocity was significantly slower in PCP-exposed workers (Triebig *et al.*, 1981). However, in the latter study, conduction velocity did not correlate with urinary levels of PCP.

Immunotoxic effects in humans as a result of chlorophenol exposure have not been convincingly demonstrated. Some woodworkers exposed to PCP reportedly had slightly increased concentrations of IgA and IgM, but levels did not correlate with exposure, and were not determined in the control group (Zober *et al.*, 1981). Hawaiian woodworkers exposed to PCP had gamma-globulin levels in the normal range (Klemmer *et al.*, 1980). McGovern (1982) observed marked T-cell suppression in patients exposed to antiseptics which contained phenols, or phenylated allergenic extracts

Chlorophenols appear to have minor effects on human blood and hematopoictic systems. Exposure to apparently high levels of PCP has been associated with symptoms of anemia (Roberts, 1981; Baader and Bauer, 1951), altered densities of leukocytes (Baader and Bauer, 1951; Enarson *et al.*, 1986 - mostly T_4CP), and assorted other hematological changes (Shirakawa *et al.*, 1959; Vinogradova *et al.*, 1973). Some recent surveys have failed to find a significant effect of PCP on the prevalence of unexplained anemias in Canadian woodworkers (Wood, 1980), or on blood parameters in Hawaiian woodworkers (Klemmer *et al.*, 1980).

Studies on woodworker exposure to chlorophenols are of particular relevance to the Canadian situation because of the widespread use of T_4CP, PCP, and their alkali salts in the lumber industry. Zober *et al.* (1981) reported on a small group of woodworkers involved in the application of PCP. Average air levels at the time of the study were 2.4 $\mu g/m^3$, the average exposure period for the cohort was 3 years and the average levels in urine and serum were 46 $\mu g/g$ creatinine and 1 $\mu g/mL$ respectively. Elevations in serum aminotransferases and γ-glutamyl transpeptidase were observed; however, confounding factors of sample size and alcohol consumption prevented any conclusions from being drawn on the impact of PCP on liver function. Woodworkers in Hawaii were studied by Klemmer *et al.* (1980) and no significant effects were reported other than respiratory tract and eye irritation. Recently Sterling *et al.* (1982) have reported on the health effects of T_4CP on 1014 woodworkers in British Columbia. Dermatological, respiratory and neurological complaints were most frequently reported and were significantly elevated in the exposure groups relative to the controls. Intensive medical assessments of 10 selected employees indicated signs of mild chronic toxicity (persistent skin rashes, headaches, respiratory disorders and pain in the extremities) in four employees.

In a subsequent study of B.C. woodworkers, Embree *et al.* (1984) identified significantly increased incidences of productive cough and decreased spirometric readings in persons exposed to T_4CP and PCP. However, symptoms were not related to the degree of exposure, leading them to conclude that they could not substantiate the findings of Sterling *et al.* (1982). In a companion report (Enarson *et al.* 1986), they noted that blood leukocyte numbers and hematocrit were decreased and urine erythrocyte concentrations increased in a dose-dependent manner.

Kleinman *et al.* (1986) and Fenske *et al.* (1987) evaluated the extent and impact of occupational exposure to Permatox 100 (20.7% 2,3,4,6-T_4CP, 3.1% PCP, plus substantial quantities of PCDDs and PCDFs) in workers from a lumber mill in Washington State. Plant air concentrations of T_4CP ranged from 0.8-12.2 $\mu g/m^3$, while no PCP was detected ($\leq 0.5 \mu g/m^3$). It was estimated that dermal exposure accounted for 95% of the total absorbed dose. Average chlorophenol concentrations in urine were higher for exposed workers than for controls (range of averages: T_4CP, exposed = 31.2-497.5 ppb, control = 6.3-28.7 ppb; PCP, exposed = 69.3-102.8 ppb, control = 28.9-38.8 ppb). In questionnaires on health effects, exposed workers complained significantly more frequently than did unexposed workers of headaches, upper respiratory irritations, eye irritations, and unusual sweating, although there was no significant correlation between urinary levels and the frequency of these symptoms. Thus, the use of chlorophenol in the wood industry is often accompanied by symptoms of mild chronic toxicity.

References to non-commercial exposures to chlorophenols, for example from treated-wood homes, or in the general population exposed to CPs from industrial accidents confirm that pulmonary, and to a lesser extent dermal, exposure to PCP can produce symptoms of poisoning similar to those documented in occupational settings. Thus minor problems of conjunctivitis, chronic sinusitis, upper respiratory complaints, recurrent headaches, neurological pain, immunotoxic effects, liver damage, skin lesions and chloracne have been reported (Anonymous, 1970, 1980; Hay, 1976; Brandt *et al.*, 1977; Gebefügi *et al.*, 1979, 1983; Ahlborg and Thunberg, 1980; Caramaschi *et al.*, 1982; Del Corno *et al.*, 1982; Favaretti *et al.*, 1982; Giambelluca *et al.*, 1982; Sangster *et al.*, 1982; Lambert *et al.*, 1986). These studies are rarely definitive and they add little to the toxicology database for chlorophenols. In general, few adverse effects can be ascribed to the low ambient concentrations to which most people are exposed, even in PCP-treated environments (Krause and Englert, 1980; Hernandez and Strassman-Sundy, 1980). Levels of exposure are discussed in Chapter F.3(a(i)).

5. Effects on Reproduction and Fetal Development

a) Effects on Animals

Chlorophenols can have reproductive and fetotoxic effects; however, they do not appear to be teratogens (Fielder, 1982; NRCC, 1982; Ahlborg and Thunberg, 1980; Kozak *et al.*,

1979). These conclusions are based primarily on the work of Schwetz *et al.* (1974a, 1974b, 1978) and of Welsh *et al.* (1987) with rats. In the former studies, technical grade PCP administered to pregnant rats on day 6 through 15 of gestation had no effect on the mother or fetus at 5.8 mg/kg b.w. per day (Schwetz *et al.*, 1974a). Fetal resorptions and a delayed development of feti were observed at 15 mg/kg b.w. per day and signs of maternal toxicity, based on weight loss, were observed at 35 mg/kg. Purified PCP had similar effects to those of technical PCP but at a lower dosage; maternal toxicity and decreased fetal weights occurred at 30 mg/kg b.w. per day and delayed development of feti was observed at the 5 mg/kg b.w. per day dose level. Neither grade of PCP was teratogenic. Courtney *et al.* (1976) also noted significant changes in rats' fetal weights with PCP exposure, but no birth defects were observed.

Purified PCP (Schwetz *et al.*, 1978) or NaPCP (Kunde and Bohme, 1978), fed to male and female rats at 26-30 mg/kg before and after mating and to females during gestation and lactation caused reductions in maternal body weight the number of offspring, neonatal body weight, neonatal survival and growth of weanlings. The no-effect level for the first study was 3 mg/kg (Table 7). Male fertility was not obviously affected (Schwetz *et al.*, 1978).

Similarly, Welsh *et al.* (1987) found that subchronic exposure of Sprague-Dawley rats to 43 mg/kg b.w. per day of purified PCP was embryolethal (this dose also reduced maternal body weight gain) and that as little as 13 mg/kg b.w. per day was fetotoxic (decreased fetal body weights and crown-rump lengths). PCP was not considered to be teratogenic in this study.

As part of a cocarcinogenicity study, Exon and Koller (1983) investigated the effects of PCP on rats exposed pre- and post-natally. Females were exposed to as much as 500 mg/kg b.w. per day of technical PCP in the feed from weaning until weaning of their offspring. A decrease in litter size and an increase in stillborn pups were recorded, but these were not significant.

It is probable that the reduced fetotoxicity of technical PCP relative to the purified material is caused by microcontaminants (NRCC, 1982). Liver enzymes which accelerate the rate of PCP metabolism can be activated by 2,3,7,8-T_4CDD (Chapter E.3). Other PCDD and PCDF microcontaminants in technical PCP may also activate microsomes and reduce the amount of fetal exposure to PCP, causing a concomitant decrease in toxicity. Indeed, it has been shown that liver enzyme activities increase upon exposure to technical, but not purified, PCP (Goldstein *et al.*, 1977).

Larsen *et al.* (1975) reported single instances of dwarfism, exencephaly, macrophthalmia and taillessness in feti after pregnant rats were fed single doses of 60 mg purified PCP per kg b.w. on days 8, 9 or 10 of gestation. These findings were, however, attributed to maternal hyperthermia, which is known to cause teratogenic effects in rats (Edwards, 1968). Hyperthermia is a common outcome of exposure to large, single doses of chlorophenols.

A limited number of studies with lower chlorophenols indicate that these compounds have weaker reproductive effects than PCP, and are also not teratogenic. Using the same protocol as in their experiment with PCP, Schwetz *et al.* (1974b) studied the effects of 2,3,4,6-T_4CP on rat reproduction. This isomer was not teratogenic, was less fetotoxic than PCP and there was no observed difference between the toxicity of the purified and technical materials. Administration of analytical grade 2,4,5-T_3CP to pregnant mice led to increased fetal resorptions and embryonic mortality at 9 mg/kg b.w. per day, but not at 0.9 mg/kg b.w. per day; no teratogenic effects were observed (Neubert and Dillman, 1972). Female rats exposed for 90 days to purified 2-MCP(500 mg/L in drinking water), 2,4-DCP (300 mg/L), and 2,4,6-T_3CP (300 mg/L) had reduced litter sizes and increased proportions of stillborn offspring relative to controls (Exon and Koller, 1985). No significant effects were exerted on birth weight, but as little as 30 mg/L of 2,4-DCP adversely affected offspring survival. Rats repeatedly exposed to as much as 1000 mg/kg b.w. of purified 2,4,6-T_3CP experienced no adverse effects on a wide variety of reproductive parameters (Blackburn *et al.*, 1986). In a fetotoxicity/teratogenicity study of numerous compounds on several strains of mice, NCI (1968) classified 2,4-DCP (subcutaneous in DMSO at 74 mg/kg b.w.) and 2,4,5-T_3CP (85 mg/kg) as compounds which were essentially inactive in this regard. *In vitro* penetration of mouse ova was depressed by 1.0 mM (163 mg/L) 2,5-, 3,4-, and 3,5-DCP, apparently by disrupting the acrosome, but not by acute *in vitro* or chronic *in vivo* exposure to 2,4-DCP (Seyler *et al.*, 1984). None of the dichlorophenols tested affected sperm motility.

b) Effects on Humans

Concern for an impact on human reproduction stems from animal studies indicating that low levels of technical PCP and H_6CDD adversely affect reproduction and fetal development (Schwetz *et al.*, 1973, 1974a). There is little information on the effects of short-term or long-term exposure to chlorophenols on reproduction in humans. Corddry (1981) has provided data on pregnancy outcomes in women married to workers from a British Columbia sawmill using NaT_4CP and NaPCP. Analysis of data from 43 women, with a total of 100 pregnancies, did not reveal any significant differences in the pregnancy outcomes of women living with exposed versus unexposed men. There was a slight trend toward more adverse pregnancy outcomes in the exposed group, but this disappeared when she corrected for alcohol consumption. Male fertility was not studied.

Other reports of human reproductive toxicity are anecdotal or incomplete. Hawaiian wood-treating employees exposed to PCP and other preservatives had slightly fewer children than nonexposed persons, but this difference was not significant, and exposure was not related to the other reproductive variables monitored (Gilbert *et al.*, 1983). Workers suffering from chloracne as a result of 15 years' exposure to a T_3CP formulation reported experiencing "decreased sexual activity" (Kleu and Goltz, 1971). Strigini *et al.* (1982) reported increases in the frequencies of birth defects and spontaneous abortions in the accident area surrounding the Seveso 2,4,5-T_3CP plant, but these correlated with the estimated T_4CDD exposure of the mothers; moreover, no data were provided.

Table 7. No-Observed-Adverse-Effect-Levels (NOAELs) established in rats exposed orally to pure, technical, and purified technical grades of chlorophenols

Chlorophenol	Sex[1]	NOAEL (mg/kg b.w. per day)	Reference
Subchronic Toxicity			
PCP Pure		3	Johnson *et al.* (1973)
PCP Purified tech.		3	Johnson *et al.* (1973)
PCP Tech.		<3	Johnson *et al.* (1973)
PCP Tech.		ca. 1.2	Knudsen *et al.* (1974)
PCP Pure		ca. 6-12[4]	Goldstein *et al.* (1977)
PCP Tech.		< (ca. 1-2)	Goldstein *et al.* (1977)
PCP Purified tech.		ca. 1	Kimbrough and Linder (1978)
PCP Tech.		<1	Kimbrough and Linder (1978)
PCP Pure	F	13	Welsh *et al.* (1987)
2,4,6-T_3CP Pure	M	500	Blackburn *et al.* (1986)
	F	500	Blackburn *et al.* (1986)
2,3,4,6-T_4CP Pure	M	50	Hattula *et al.* (1981a)
Teratogenicity/Fetotoxicity			
PCP Tech.[2]	M,F (progeny)	5	Schwetz *et al.* (1974a)
PCP Purified tech.[2]	M,F (progeny)	<5	Schwetz *et al.* (1974a)
PCP Purified tech.[3]	M,F	3	Schwetz *et al.* (1978)
PCP Pure	M,F (progeny)	4	Welsh *et al.* (1987)
T_4CP Tech.[2]	M,F (progeny)	10	Schwetz *et al.* (1974b)
T_4CP Purified	M,F (progeny)	10	Schwetz *et al.* (1974b)
2,4,5-T_3CP Pure	M,F (progeny)	0.9	Neubert and Dillman (1972)
Chronic Toxicity			
PCP Purified tech.	F	3	Schwetz *et al.* (1978)
	M	10	Schwetz *et al.* (1978)
Carcinogenicity			
PCP Purified tech.	F	30	Schwetz *et al.* (1978)
PCP Purified tech.	M	30	Schwetz *et al.* (1978)

1. Males (M), females (F).
2. Studies based on exposures during days 6 to 15 of gestation.
3. Studies based on exposures for 62 days before mating, for 15 days during mating, and subsequently throughout gestation and up to lactation.
4. Approximate range interpolated from figure in publication. Dose (as mg/kg b.w. per day) fell off monotonically throughout the study.

6. Chronic Toxicity

a) Effects on Animals

Very few true "chronic" (i.e. lifetime) studies of the effects of chlorophenols have been undertaken. Schwetz *et al.* (1978) have reported on a two-year exposure of rats to purified PCP (Table 7). In females, Schwetz *et al.* reported no toxic effects observed at 3 mg/kg b.w. per day or less, liver and kidney pigment accumulation at 10 mg/kg, and decreased body weight gain, increased serum glutamic pyruvic transaminase (GPT) activity and pigment accumulation at 30 mg/kg b.w. per day. Fewer changes were observed in male rats: no effects were observed below 30 mg/kg b.w. per day, the level at which pigment accumulation and increased GPT activity were reported. No absolute or relative weight increase in liver weight occurred at 30 mg/kg b.w. per day, in spite of the fact that Johnson *et al.* (1973) reported increased weights of this tissue in male and female rats after subchronic exposure to 30 mg/kg b.w. per day of the same purified PCP.

Other chronic studies in animals have been designed specifically to evaluate the carcinogenic properties of chlorophenols and are reported in a subsequent section. While the scarcity of chronic toxicity data hampers the assessment of the import of the higher chlorinated phenols, subchronic exposure studies of rats and other laboratory animals have yielded much toxicology data for PCP and T_4CP. Knowledge of the chronic toxicity of the lower chlorinated phenols is lacking.

b) Effects on Humans

There are few published studies of the effects of life-time exposure to these chemicals. The high rate of employee turnover, along with variation in the level and duration of exposure make distinguishing between subchronic and chronic human-exposure difficult. The results of published studies of the effects on humans of long-term exposure to chlorophenols have been described in Section 4(b) in this chapter, while the issue of the carcinogenicity of chlorophenols is addressed in the next section.

It is clear that PCP production facilities have led to significant worker exposure (Section 4(b)). Other than chloracne in some heavily exposed workers, few signs of toxicity have been reported in workers exposed to chlorophenols for long periods. Arsenault (1976) has reported the results of a prospective clinical evaluation of 21 PCP workers involved in the pressure-treatment of wood. These workers had been exposed on average for 9 years and had blood serum PCP levels of 1.05 ppm. Control workers had approximately 0.1 ppm PCP in blood serum. The only significant clinical findings in the pressure-treatment workers were vertigo and insomnia. Cases of conjunctivitis and skin disorders were reported in company health records for the period 1961-1971.

Klemmer *et al.* (1980) have reported the results of a 7-year study of more than 400 Hawaiians, many of whom had long-term, high-level exposures to PCP. Concentrations of PCP in blood serum far exceeded those reported in Arsenault's (1976) study; open-vat wood-treaters had a mean level of 3.78 ppm PCP; pressure-tank workers, 1.72 ppm and farmers and controls 0.25 and 0.32 ppm respectively. After considering data on 189 individuals of the total of 400 Klemmer *et al.* concluded... "despite high chronic exposures to PCP, individuals in the wood-treatment group of workers had not undergone any serious health effects from this exposure. The only evidence of tangible health effects, part of which could have been caused by exposures to chemicals other than PCP, were the low-grade infections or inflammations of the skin and subcutaneous tissue, of the protective membrane of the eye, and of the mucous membrane of the upper respiratory tract. No specific long-term effects could be elicited in the exposed group". Takahashi *et al.* (1976) observed similar plasma PCP levels in occupationally exposed workers (controls 0.07 ppm, exposed 3.41 ppm), presumably Hawaiian. Exposure was accompanied by significantly elevated levels of C-reactive protein (a general indicator of inflammatory disorders or tissue damage), total bilirubin, creatinine phosphokinase, and $\alpha 2$-globulin, while liver enzyme activities and other serum protein levels were unaffected.

7. Carcinogenicity

a) Effects on Animals

The carcinogenicity of chlorophenols is a contentious issue. The International Agency for Research on Cancer has reviewed the data available on the carcinogenic properties of PCP (IARC, 1979a), and 2,4,5- and 2,4,6- T_3CP (IARC, 1979b) and concluded that the published data was inadequate to evaluate the carcinogenicity of PCP and 2,4,5-T_3CP because of small sample sizes, or design problems. The published evidence suggests that PCP is not an animal carcinogen or a tumorigen, and does not serve to promote tumor formation by other compounds. There is sufficient evidence that 2,4,6-T_3CP is an animal carcinogen under some conditions, but not a promoter. The other chlorophenols have not been tested for their carcinogenic properties, but several of them may be tumor-promoters in the presence of an initiating agent.

The results of two carcinogenicity bioassays on PCP have been published. Innes *et al.* (1969) exposed two strains of mice (72 animals in total) to roughly the maximum tolerated dose for a total of 78 weeks, and did not find any significant increases in tumor incidences in males and females of either strain. Schwetz *et al.* (1978) reported similar findings in rats exposed to a maximum of 30 mg/kg b.w. per day technical PCP for 24 months. Using these data the Carcinogenic Assessment Group of the USEPA concluded that PCP was negative with respect to oncogenic effects (Williams, 1982).

The carcinogenicity of PCP (technical and commercial grade) has recently been tested by the National Toxicology Program of the US Department of Health and Human Services; however, their evaluation of the results is not yet complete.

To test the carcinogenicity of 2,4,6-T_3CP, NCI (1979) dosed rats and mice with as much as 10 000 mg T_3CP/kg of feed (96-97% pure) for 106 and 105 weeks respectively. At the end of the study, the dosed male rats had an increased incidence

of lymphomas and leukemias, while leukocytosis and monocytosis of the peripheral blood and hyperplasia of the bone-marrow were found in those that did not show lymphomas and leukemia. In female rats, no lymphomas or leukemias were detected, but leukocytosis and monocytosis of peripheral blood and bone-marrow hyperplasia were evident. Both the male and female mice displayed a dose-related incidence of hepatocellular carcinoma or adenoma. In contrast, Innes *et al.* (1969) did not observe significant increases in tumor formation in mice chronically fed 2,4,6-T_3CP at the maximum tolerated dose; however, the sample size was somewhat limited, and they did note slight elevations in the frequencies of hepatoma and reticulum-cell sarcoma.

Exon and Koller (1981, 1985) carried out 15-24 month studies on rats exposed both pre- and post-natally to 2-MCP, 2,4-DCP or PCP (see also Chapter E.5.(a)). No evidence of tumor initiation was revealed at the dose levels of up to 500 mg/kg of 2-MCP or PCP (Exon and Koller, 1981) or 300 mg/L of 2,4-DCP (Exon and Koller, 1985) given in the drinking water. However, 2-MCP acted as a promoter of carcinogenic activity by ethylnitrosourea (ENU), reducing tumor latency and increasing tumor incidence relative to controls receiving only ENU.

Tumor promotion studies of phenol and chlorophenols using dimethylbenzanthracene (DMBA) as the initiator on mouse skin indicated that phenol, 2-MCP, 2,4-DCP and 2,4,5-T_3CP were probable tumor promoters but that 2,4,6-T_3CP and higher chlorophenols were not (Boutwell and Bosch, 1959). None of the chlorophenols tested were tumorigenic when applied alone.

b) Effects on Humans

The question of whether there may be carcinogenic effects of chlorophenols on humans is not resolved. There is mounting evidence that workers exposed to technical grade chlorophenols and their by-products or derivatives, especially dioxins and phenoxyacetic acids, have an increased risk of developing soft-tissue sarcomas and lymphomas. IARC (1986) has recently concluded that there is "limited evidence" that occupational exposure to chlorophenols is carcinogenic to humans.

Considerable debate has ensued since the initial reports of chlorophenol-related cancer by Hardell (1977, 1979) and the subsequent reports of Hardell and his co-workers in Sweden. Case-control studies of patients with soft-tissue sarcoma in Sweden indicated a relative risk (RR) of 6.6 for those exposed to chlorophenols, primarily T_3CP, compared to those who did not appear to have been exposed (Hardell and Sandstrom, 1979). Individuals exposed to 2,4,5-T had an RR of 5.8. A follow-up study in another area of Sweden confirmed the overall risk of soft-tissue sarcomas in individuals exposed to phenoxy herbicides or chlorophenols, yielding RR values of 6.8 and 3.3 respectively (Eriksson *et al.* 1981). Hardell *et al.* (1981) also applied their case-control technique to malignant lymphoma patients in Sweden, deriving RR values in individuals exposed to phenoxy herbicides, chlorophenols and organic solvents of 4.8, 4.3 and 2.4 respectively. The RR value for high-level exposure to chlorophenols was 7.6. A possible explanation for the lymphomas may rest with the immunological effects (in animals) of the dioxin contaminants. Some immunosuppressive drugs are known to increase the incidence of histiocytic type lymphomas in humans (Hardell, 1979).

In testimony before the USEPA on behalf of the Dow Chemical Company, Cole (1980) was intensely critical of the Swedish studies and dismissed several studies that show positive correlations between cancers and phenoxy acids, primarily on the basis of observer and recall bias. Instead, he accepted as useful three North American investigations (Cook *et al.*, 1980; Ott *et al.*, 1980; Zack and Suskind, 1980), that indicate *no* correlations between cancers and 2,4,5-T exposure, although each had very small sample sizes.

Cole's criticisms have since lost credibility. First, Hardell (1981) applied his case-control method to study colon cancer, a disease that correlates positively with asbestos levels, and re-evaluated his original data on soft-tissue sarcoma to address the issue of recall bias. He found that colon cancers correlated significantly only with exposure to asbestos, but not phenoxy acids or chlorophenols, and concluded that recall and observer bias were negligible in his earlier studies. In addition, Honchar and Halperin (1981) re-evaluated the studies with negative findings that Cole (1980) judged as useful, and found an unrecognized excess of soft-tissue sarcomas in the aggregate total of 105 workers from the combined studies. Finally, subsequent reports of a relation between phenoxy acid and/or chlorophenol exposure and the incidences of soft-tissue sarcomas, malignant lymphomas, or other cancers (Axelson *et al.*, 1980; Hardell and Eriksson, 1981; Johnson *et al.*, 1981; Moses and Selikoff, 1981; Hardell and Axelson, 1982; Thiess *et al.*, 1982; Hardell *et al.*, 1982; Gallagher and Threlfall, 1984; Woods *et al.*, 1987) have confirmed the findings of the earlier studies. However, while there is mounting evidence that exposure to the technical grades of lower chlorophenols is associated with elevations in the rates of certain cancers, there is no clear cut dose-effect relationship. "Exposure" has been loosely defined and no quantitative assessments have been published. Further, some recent case-control studies have failed to identify an association between chlorophenol exposure and the incidences of various cancers. Smith *et al.* (1984) and Pearce *et al.* (1986) determined nonsignificant odds ratios for soft-tissue sarcomas and non-Hodgkin's lymphomas respectively among New Zealand sawmill workers, and the former study was unable to attribute significant ratios for meat and tannery workers and for fence construction unambiguously to chlorophenol exposure. In a Finnish survey for association between respiratory cancers and exposures in the particleboard, plywood, sawmill or formaldehyde glue industries, odds ratios for chlorophenol exposure were not significant (Kauppinen *et al.*, 1986). Tola *et al.* (1980) and Olsen and Jensen (1984) did not find a significant relationship between nasal cancers and chlorophenol exposure among workers from a variety of industries in Finland and Denmark respectively. Woods *et al.* (1987) discussed possible reasons for

the inconsistencies among some of these studies and presented evidence that they were in part attributable to differences in the short-term intensity of exposure.

Only two brief references to PCP exposure and human cancer are available. Greene *et al.* (1978) have suggested there may be an association between exposure to wood treatment chemicals (PCP) and Hodgkin's disease. Bishop and Jones (1981) reported two cases of non-Hodgkin's lymphoma in PCP workers in Britain; both cases were associated with chloracne. These data are inadequate to identify a positive and statistically sound correlation between lymphomas and PCP. More study of this important topic is warranted.

8. Mutagenic and Cytogenetic Effects

a) Effects on Animals

Williams (1982) and Fielder (1982) have both reviewed current literature on the mutagenic and cytogenetic effects of PCP. Although shortcomings in the available information and in some assays make any conclusion tentative (Fielder, 1982), chlorophenols do not appear to have potent mutagenic or cytogenetic effects. The Ames *Salmonella typhimurium* test (Andersen *et al.*, 1972; Lemma and Ames, 1974), a sex-linked lethal test with *Drosophila melanogaster* (Vogel and Chandler, 1974) and a host-mediated assay (Schwetz *et al.*, 1978) all indicate that PCP probably does not cause point mutations. A mammalian spot-test did not reveal any significant mutagenic activity in mice (Fahrig *et al.*, 1978). An *in vitro* study to show primary damage using *Saccharomyces cerevisiae*, however, demonstrated an increase in mitotic gene conversion (Fahrig *et al.*, 1978; Fahrig, 1974), and sodium pentachlorophenate (20 mM) reportedly increased the frequency of both auxotrophic and morphological variations in the fungus *Aspergillus niger* 350 (Roy *et al.*, 1981). Findings in an *in vivo* mammalian dominant lethal test were negative (Buselmaier *et al.*, 1973), suggesting that PCP does not cause chromosomal aberrations. However, exposure to concentrated solutions of PCP increased the incidence of "stickiness", lag chromosomes, fragmented chromosomes, and other chromosomal aberrations in *Vicia faba* meiotic flower bud and mitotic lateral root cells (Amer and Ali, 1968, 1969, 1974).

The unsaturated chlorophenols also appear to have mild mutagenic and cytogenetic effects, although the available information is limited. Räsänen *et al.* (1977) found that none of the chlorophenols tested (all dichlorophenol isomers, four of six trichlorophenols, and 2,3,4,6-tetrachlorophenol) caused point mutations in the Ames *Salmonella typhimurium* test, but did not regard a negative result with this test as conclusive. Another test with *Salmonella* identified 4-MCP as a weak mutagen (Seuferer *et al.*, 1979). Pure 2,4,6-T_3CP (400 mg/L) caused a weak but significant increase in the frequency of forward mutations, but did not affect intergenic or intragenic recombination in the yeast *Saccharomyces cerevisiae* (Fahrig *et al.*, 1978). Pregnant mice injected with 50 and 100 mg/kg b.w. of 2,4,6-T_3CP on day 10 of gestation displayed a slightly increased frequency of spotted coat in the offspring, indicative of a weak mutagenic activity (Fahrig *et al.*, 1978). Amer and Ali (1968, 1969, 1974) reported that 4-MCP and 2,4-DCP produced the same chromosomal aberrations in *Vicia faba* that were observed in the experiments with PCP described previously. Finally, pea seedlings soaked in 60 ppm of 2,4-DCP had inhibited spindle formation and signs of prophase poisoning, with consequent suppression of mitosis (Mühling *et al.*, 1960).

b) Effects on Humans

In one study, lymphocytes taken from workers at a PCP plant had a small but significantly higher incidence of dicentric and acentric mitoses (Bauchinger *et al.*, 1982). However, in other instances peripheral blood cells in groups of workers exposed to PCP have not revealed significantly greater incidences of chromosomal abnormalities (Wyllie *et al.*, 1975; Ziemsen *et al.*, 1987). PCP did not cause single-strand breaks in human fibroblast DNA, but its metabolite tetrachlorohydroquinone demonstrated this ability (Witte *et al.*, 1985).

One study has addressed the cytogenetic effects of 2,4,5-T_3CP in humans. Lymphocytes cultured from English workers ten years after accidental exposure to the technical product did not display a significant increase in the frequency of chromosomal aberrations (Blank *et al.*, 1983).

9. Toxicity of Chlorophenol Impurities

Commercial chlorinated phenols contain a wide range of contaminants. Concentrations are usually in the ppm range, hence these compounds are often referred to as 'microcontaminants'. The amounts and identities of these microcontaminants, which can vary tremendously in concentration from one product to the next and from batch to batch, were discussed in an earlier chapter (see B.4.).

Concern for the toxic effects of microcontaminants has focused on the dioxins because of the extreme toxicity of 2,3,7,8-T_4CDD. However, this congener occurs principally in 2,4,5-T_3CP (Firestone *et al.*, 1972). MCP and DCP are not reported to contain detectable levels of chlorinated dioxins. PCP and T_4CP contain isomeric forms of OCDD, H_7CDD and H_6CDD and low part-per-billion concentrations of P_5CDD and T_4CDD (Rappe *et al.*, 1982; Hagenmaier, 1986; Hagenmaier and Brunner, 1987); in the latter reports, extremely low levels of 2,3,7,8-T_4CDD were detected in some commercial NaPCP and 2,3,4,5-T_4CP products from Europe.

A brief summary of the toxic properties of the microcontaminants of chlorophenols is provided in this section. Reviews of dioxin toxicology and residue levels are available in Fielder (1982), Hutzinger *et al.* (1981), Kociba and Schwetz (1982), Jones (1981) and NRCC (1981, 1984).

a) Polychlorinated Dibenzo-p-dioxins

In general, PCP and T_4CP contain <100 ppm H_6CDD, <200 ppm H_7CDD and <2000 ppm OCDD, with recent formulations containing relatively low levels (Chapter B.4). Fortunately the most toxic of these three homologues, H_6CDD, is found in the lowest concentration.

(i) Octachlorodibenzo-p-dioxin

Only one congener exists of this fully substituted isomer. It has not been found to be acutely toxic to rats when administered orally at 1 mg/kg b.w., nor was it acnegenic to rabbits when applied as a 10% solution in chloroform. Subacute exposures of approximately 1 mg/kg b.w. per day for 3 weeks caused no toxic signs. Livers were nominally enlarged but appeared normal under the light microscope. OCDD does not appear to be mutagenic in the Ames test and has not undergone a carcinogenicity bioassay. It was not teratogenic at 500 µg/kg per day or fetotoxic at 100 µg/kg per day when administered to female rats on days 6 to 15 of gestation (Fielder, 1982).

(ii) Heptachlorodibenzo-p-dioxins

There is a paucity of data available on H_7CDD. The LD_{50} value has not been determined accurately for either of the possible isomers.

(iii) Hexachlorodibenzo-p-dioxins

Commercial PCP and Na-PCP have been found to contain four of 10 possible H_6CDD isomers, of which the 1,2,3,6,8,9 and 1,2,3,6,7,8 isomers predominate (Fielder, 1982). Levels are in the <1-4 ppm range in recent commercial samples of PCP and Na-PCP (Chapter B.4). The acute oral toxicity (LD_{50}) of 1,2,3,6,7,8-H_6CDD in the mouse is 1250 µg/kg (Table 8). H_6CDD is more toxic to female rats and mice than to males. Signs of toxicity include weight loss, deterioration of skin, and delayed mortality, with death occurring as late as three weeks. Thymus, liver, spleen, kidney and testes are affected by H_6CDD. This isomer is also known to be acnegenic.

Subacute exposure of rats to H_6CDD isomers indicated no-observed-effect- levels for the rat of <2.5 µg/kg per week and for the mouse of <1.2µg/kg per week (NCI, 1980a). Above these levels weight loss and liver damage were observed. Dermal exposure of mice to H_6CDD also resulted in liver damage and mortality, even at the lowest dose of 1.5 µg/kg per week (NCI, 1980b). Thus, H_6CDD is readily absorbed by skin and extremely toxic. A mixture of 1,2,3,6,7,8- and 1,2,3,7,8,9-H_6CDD administered orally increased the incidence of hepatocellular carcinomas or adenomas in female rats, and mice of both sexes; however, male rats did not develop hepatocellular carcinomas or adenomas in excess of the control rate (NCI, 1980a). Carcinogenicity assays using dermal exposures were inconclusive (NCI, 1980b).

Based on exposure of pregnant rats to an unidentified mixture of H_6CDD isomers, this homologue is considered fetotoxic and teratogenic (Schwetz *et al.*, 1973). The no-observed-adverse-effect-level was 0.1 µg/kg per day. Cleft palate, vertebrae with split or unfused centra and split sternebrae were observed in feti of females fed 100 µg/kg per day on days 6 to 15 of gestation. Fetal resorptions were observed at maternal doses of 10 µg/kg per day and fetal edema at doses of ≥1 µg/kg per day.

(iv) Pentachlorodibenzo-p-dioxins

Little is known of the toxicity of this homologue. One of the 14 isomers, namely 1,2,3,7,8-P_5CDD, is extremely toxic (Rappe *et al.*, 1982).

(v) Tetrachlorodibenzo-p-dioxins

There are 22 isomers of T_4CDD, and of them 2,3,7,8-T_4CDD is the most toxic. T_4CDD isomers have been reported in commercial T_3CP; however, these chlorophenols are not manufactured in Canada, and quantities imported for use are relatively small (Chapter C.1)

In general dibenzo-p-dioxins with chlorines in the 2,3,7 and 8 positions of the molecule are the most toxic isomers to animals. 2,3,7,8-T_4CDD is the most acutely toxic dioxin known; mean oral LD_{50} values range from 0.6 µg/kg b.w. in the guinea pig to 3 mg/kg b.w. in the hamster. Like H_6CDD, there is a delayed mortality associated with single acute exposures. Acute and subacute exposures of human and non-human primates have resulted in hair loss, chloracne, weakness, loss of body weight and neurological signs. Other animal studies have indicated additional signs of toxicity including hypothyroidism, porphyria and pancytopenia. Tissue lesions associated with exposure to 2,3,7,8-T_4CDD are found in thymus, testes, bladder and liver. There is mounting evidence that 2,3,7,8-T_4CDD is immunotoxic (NRCC, 1981).

2,3,7,8-T_4CDD also appears to be teratogenic and fetotoxic. Studies with rats have indicated that it affects breeding success in both the F_0 and F_1 generations. The lowest-effect-level in rats is 0.01 µg/kg b.w. per day and probably close to this dose in rhesus monkeys (NRCC, 1981). Another T_4CDD congener, 1,2,3,4-T_4CDD had no prenatal or postnatal effects when administered to pregnant rats at 0.8 mg/kg b.w. per day during gestation (Khera and Ruddick, 1973) or to mice at up to 1 mg/kg b.w. per day (Courtney, 1976).

2,3,7,8-T_4CDD is carcinogenic for mice and rats, producing hepatic carcinomas and neoplastic nodules in both sexes. Females are more sensitive than males, a pattern which is also apparent with H_6CDD exposure. The lowest effect level in female rats is 0.01 µg/kg b.w. per day, more than an order of magnitude less than the effect level in female rats fed H_6CDD, i.e. 0.36 µg/kg b.w. per day. These data indicate that 2,3,7,8-TCDD is a carcinogen; however, it is not a potent mutagen (NRCC, 1981).

Table 8. Summary of toxicology data for H_6CDD

Exposure	Species	Vehicle[1]	Isomer[2]	Route	Toxicity/Sex	Observations	Reference
Acute							
Lethality							
(LD_{50})	Rat	CO:Acetone	B/C mix	Oral	800 µg/kg ♀ 1800 µg/kg ♂	Similar observations in all studies	NCI, 1980a
	Mouse	CO:Acetone	B/C mix	Oral	500 µg/kg ♀ 750 µg/kg ♂	Weight loss, skin eruptions, delayed	NCI, 1980a
		CO	A	Oral	825 µg/kg	death. Tissues affected:	McConnell *et al.*, 1978
		CO	B	Oral	1250 µg/kg ♀,♂	liver, thymus, spleen,	
		CO	C	Oral	1440 µg/kg	kidney, testes.	
	G. Pig	CO	A	Oral	73 µg/kg		McConnell *et al.*, 1978
		CO	B	Oral	70-100 µg/kg ♀,♂		
		CO	C	Oral	60-100 µg/kg		
Subacute/Subchronic							
Toxicity							
(NOAEL)	Rat	CO:Acetone	B/C mix	Oral	<2.5µg/kg per wk ♀,♂	Thymic atrophy, splenic hypertrophy, liver lesion at 10-50 µg/kg per week.	NCI, 1980a
	Mouse	CO:Acetone	B/C mix	Oral	1.2 µg/kg per wk ♀,♂	Only liver damage at higher levels (10-50 µg/kg per week).	NCI, 1980a
		Acetone		Dermal	<1.5 µg/kg per wk ♀,♂		NCI, 1980b.
Fetal Tox.							
(NOAEL)	Rat	CO:Acetone		Oral	0.1 µg/kg per day	Fetal edema 1 µg/kg resorptions10 µg/kg terrata and maternal toxicity 100 µg/kg.	Schwetz *et al.*, 1973
Chronic							
Carcin.							
Bioassay	Rat	CO:Acetone	B/C mix	Oral	positive for ♀ 1.25 µg/kg per wk	Loss of body weight (♂ and ♀). Hepatocellular carcinomas and neoplastic nodules in ♀ only.	NCI, 1980a
	Mouse	CO:Acetone	B/C mix	Oral	positive for ♀ 10 µg/kg per wk. positive for ♂ 5 µg/kg per week	Hepatocellular carcinomas and adenomas.	
		Acetone	B/C mix	Dermal	inconclusive in ♂,♀	Fibrosarcomas observed in ♀. Incidence nonsignificant.	NCI, 1980b

1. Vehicle: CO = Corn oil; CO:Acetone = 9:1 mixture corn oil and acetone.
2. Isomers: A = 1,2,3,4,7,8-H_6CDD; B = 1,2,3,6,7,8-H_6CDD; C = 1,2,3,7,8,9-H_6CDD.

(vi) Tri-,Di- and Monochlorodibenzo-p-dioxins

There are occasional reports of T_3CDD and DCDD in the lower chlorinated phenols and some of their manufactured products but not of MCDD. DCDD has very low acute oral toxicity; the LD_{50} is >1 g/kg b.w. per day in the rat and higher in the mouse (Schwetz *et al.*, 1973). 2,7-DCDD has been fed to mice and rats for long periods at dosages up to 2.5 g/kg b.w. per day and 750 mg/kg b.w. per day respectively without any clear indication of exposure-related cancer. No teratogenic effects have been reported in feti of rats fed 100 mg 2,7-DCDD/kg b.w. per day (NRCC, 1981). There is no information on the effects of exposure to T_3CDD or MCDD.

b) Polychlorinated Dibenzofurans

Little is known of PCDF toxicity despite their relatively common presence in chlorophenols at levels of 1-500 ppm. Some congeners have considerable acute oral toxicity. For example the LD_{50} of 2,3,7,8-T_4CDF in guinea pigs and monkeys is 5-10 µg/kg b.w. and 1 mg/kg b.w., respectively (NRCC, 1984). Rappe *et al.* (1982) indicate that 1,2,3,7,8-P_5CDF, 2,3,4,7,8-P_5CDF and 2,3,4,6,7,8-H_6CDF all have LD_{50} values in the range of 1-100 µg/kg b.w. in the most sensitive species tested. Like dioxins, the toxicity of PCDF isomers is highest for those with chlorine atoms in the 2,3,7 and 8 positions of the molecule. Metabolism of these lipophilic microcontaminants is also related to the position and number of chlorine atoms. 2,3,7,8-T_4CDF and 2,3,4,7,8-P_5CDF appear to have the longest half-lives of the PCDFs studied (Masuda and Kuroki, 1982). Furthermore, these authors have suggested that PCDFs, especially the tetra and penta isomers, may have been largely responsible for the signs of Yusho disease reported in Japanese who ingested rice oil contaminated with PCBs, PCDF and polychlorinated quaterphenyls (PCQs). PCDFs have acnegenic properties but may not be porphyrinogenic.

c) Polychlorinated Diphenylethers

Polychlorodiphenyl ethers (PCDPEs) are common contaminants of chlorophenols which are found almost exclusively in T_4CP and PCP (Jones, 1981). Little is known of their toxicology.

d) Other Microcontaminants

Less common impurities of chlorophenols include polychlorinated phenoxyphenols (PCPPs, also known as 'predioxins' or 'isopredioxins'), polychlorinated biphenyls (PCBs) and polychlorinated benzenes (Jones, 1981). Extensive toxicology data exist on the effects of PCBs (WHO, 1976) and some members of the chlorinated benzene group, i.e., hexachlorobenzene (HCB) (IARC, 1979c). Although these two groups of chemicals are not very acutely toxic, they can affect reproduction and are considered carcinogenic. Both contain chlorinated dioxin and furan impurities.

F. Hazard Assessment

1. Introduction

The hazard assessment provided in this report pertains to the use of chlorophenols in Canada. The hazards associated with chlorophenol exposure are related to their individual and collective toxicity, as defined in experimental studies, and to the degree of exposure of persons in occupational and non-occupational settings. Hazard assessments for chlorophenols (as for any chemical substance) are arbitrary and arguable for a number of reasons. First,there are few precise exposure data available for occupational settings in Canada, and there is only slightly more quantitative information on levels of chlorophenols in the environment that are relevant to human-exposure scenarios. Some inferences can be drawn from data available in other countries, especially the USA, where product type, lifestyle and occupational standards tend to be similar to those in Canada. Second, it is rare to find studies that equate specific exposures with specific states of health. Finally, epidemiological investigations that are retrospective in nature are useful in providing data on long-term health effects, but exposures are nearly always considered qualitatively, for example as when exposure is based on job title or address.

2. Occupational Exposure

a) Toxicologic Considerations

Some past uses of chlorophenols posed a significant hazard to specific aspects of the health of workers employed in the production, manufacture or use of these chemicals (Chapter E). Chloracne, skin rashes, neurological and respiratory conditions, headaches, nausea and weakness have been documented in employees at numerous production and manufacturing sites. Acute intoxications leading to hyperpyrexia and death have been repeatedly associated with occupational chlorophenol overexposure and are caused by the chlorophenol itself rather than its microcontaminants. Chloracne appears to be an effect of the chlorinated dibenzo-p-dioxins and furans found in chlorophenols.

Changes in industrial practice have resulted in fewer high-dosage, acute exposures. The last reported PCP-related mortality in Canada in an occupational setting was in 1963, in which one fatality and four cases of extreme morbidity occurred in workers hand-dipping window sashes in 4.1% PCP solution (Bergner *et al.*, 1965). However, short- and long-term low-level exposures have continued, and recent reports of workers' complaints in two Canadian sawmills indicate that persistent and transitory respiratory, dermatological and neurological conditions occur in some sawmill workers using Na-T_4CP (Sterling *et al.*, 1982). These same symptoms as a result of PCP exposure have been documented in earlier studies, which were reviewed by Fielder (1982).

Studies designed to examine changes in woodworkers exposed to PCP and T_4CP for extended periods have failed to indicate statistically significant effects on major organs, nerves, blood, reproduction or the immune system (Fielder, 1982; Corddry, 1981; Triebig *et al.*, 1981; Wood, 1980; Zober *et al.*, 1981; Klemmer *et al.*, 1980; Arsenault, 1976; Wyllie *et al.*, 1975 - but see Enarson *et al.*, 1986). However, many of these studies have suffered from small sample sizes, and as a result real effects on such parameters as liver enzymes, kidney function, T-cells and nerve conduction velocity reported by some of the above authors may not be statistically significant. Other studies have been nonspecific in searching for signs of intoxication in large groups of employees. In the aggregate these studies do indicate that chronic exposure to relatively high levels of PCP or T_4CP leading to mean blood plasma concentrations as high as 4 ppm (Klemmer *et al.*, 1980) is likely to be causing borderline effects on some physiological functions. Some of these effects, especially those involving the liver and the immune system, may be caused in whole or in part by the microcontaminants of these chlorophenols, especially H_6CDD.

Swedish reports of increased incidences of soft-tissue sarcomas and lymphomas in 'chlorophenol-exposed' workers have gained credibility in Europe and the USA (see Chapter E.7(b)). Prior to its ban on the use of chlorophenols for wood treatment in 1978 (Ahlborg and Thunberg, 1980) Sweden produced 2,4,6-T_3CP, and used it together with PCP and T_4CP for the treatment of fresh cut lumber. 2,4,5-T_3CP was also produced in Sweden for use in the manufacture of phenoxy herbicides. 2,4,6-T_3CP is considered to be an animal carcinogen, while commercial formulations of 2,4,5-T_3CP are known to contain the carcinogenic 2,3,7,8-T_4CDD. The major deficiency in these studies does not appear to be observer and recall bias during questionnaire administration but rather the lack of specific exposure data.

The applicability of the Swedish findings for Canadian woodworkers is in question for two reasons. First, T_3CPs have never been produced in Canada, nor were they used much in the lumber industry here (Jones, 1981), which instead employs T_4CP, PCP, and their sodium salts. Second, PCP is not considered to be carcinogenic to animals, although the available data are quite limited (Chapter E.7). T_4CP has not been tested but contains similar levels of microcontaminants to PCP (Table 3; Rappe *et al*, 1979; Cedar, 1984), and is thus unlikely to be

highly carcinogenic to animals. This issue of a threat of cancer from long-term exposure to PCP and T_4CP in Canada will remain unresolved until an ongoing NHW-sponsored retrospective study of morbidity and mortality on Canadians employed in sawmills and pressure-treatment facilities using these chlorophenols is completed.

The principal routes of occupational exposure to chlorophenols in Canada are inhalation and dermal absorption. Since chlorophenols are no longer produced in Canada (Chapter C.1), the majority of occupational exposure is to PCP and T_4CP in the lumber industry. Application techniques in this industry such as dipping, spraying and pressure treating may increase the volatilization of PCP and the potential for dermal contact. Although the amounts of chlorophenols used for surface treatment of lumber are minor compared to quantities used for pressure treatment, application of anti-sapstains can result in considerable human exposure and environmental contamination. Small or old mills still employ large open dip-tanks. Lumber being prepared for stockpiling or shipment is frequently dipped by fork-lift truck operators into vats of anti-sapstain solution and then driven dripping across the storage site.

Airborne levels of PCP have been reported for sectors of the wood treatment industry, primarily in the USA (Table 9), and in most cases are below the 0.5 mg/m^3 $TLV^{(R)}$ of the American Conference of Governmental Industrial Hygienists (ACGIH, 1986). Pulmonary and dermal exposures have resulted in low ppm concentrations of PCP or T_4CP in the plasma and urine of occupationally exposed persons (Table 9; Chapter E.4.b); the highest concentrations in body fluids are found in persons having dermal contact with treated lumber or contaminated equipment. Sangster *et al.* (1982) summarized that plasma levels of PCP in non-occupationally exposed individuals are in the <0.5 to 1.0 mg/L range, 1 to 10 mg/L in the occupationally exposed and >40 mg/L in obviously intoxicated persons. The more recent data in Table 9 suggest that the first two ranges are somewhat high, perhaps as a result of improvements in industrial hygiene and restrictions on the uses of chlorophenols.

Despite reports of ppm concentrations of PCP in human body-fluids, chlorophenols do not appear to concentrate in human tissue or fluids relative to ambient exposure levels. In fact, measured levels are a reflection of the degree of exposure (e.g. Kleinman *et al.*, 1986) and decrease rapidly after exposure is reduced (Chapter E.3).

The available exposure data are static, and as such give no information on the actual burden of chlorophenols that a worker is taking up. Calculations of theoretical exposures have been provided in several reviews (NRCC, 1982; Williams, 1982; Kozak *et al.*, 1979; Arsenault, 1976). However, there is some indication that the models on which these exposures are based seriously underestimate worker exposure by ignoring dermal uptake. While Kozak *et al.* (1979) reported a rough agreement between total airborne exposure and urinary excretion, calculations of exposure and excretion values from the data provided in Table 10 do not indicate a 1:1 correspondence between published airborne PCP concentrations and urine levels. Urinary excretion is 4 to 20 times higher than estimated exposure, suggesting either that other routes of exposure contribute significantly to total exposure (Fenske *et al.* (1987) reported that 95% of exposure of American sawmill workers to T_4CP and PCP was dermal), or that employees were exposed to far higher concentrations of airborne PCP prior to or during the study period than reported.

Instead, exposure can be better estimated from the total (conjugated plus free) concentration of chlorophenols in urine. In a recent study of employees in the Canadian wood-preservation industry, Currie and McDonald (1986) found the highest concentrations of PCP in the urine of a sawmill grader, who had as much as 0.293 mg of total PCP per litre. Assuming that the sawmill grader produces 1.4 L of urine daily, and that urinary excretion equals 86% of the systemic dose (Braun *et al.*, 1978, 1979), this corresponds to an estimated daily dose of 477 µg per day, or 6.81 µg per kg b.w. per day for a 70 kg sawmill grader. This exposure is more than double the ADI of 3 µg/kg b.w. per day calculated by the National Academy of Sciences (1977), based on data from a subchronic feeding study in rats (Johnson *et al.*, 1973) and a 1000-fold safety factor. Given that PCP concentrations in most of the urine samples analyzed by Currie and MacDonald, including others from the same job category, were one to two orders of magnitude below this level, and that the ADI incorporates a 1000-fold safety factor, this exposure is unlikely to present a significant hazard. However, certain job categories often have urine PCP concentrations that indicate exposure near this ADI, and some of the chlorophenate solutions used may contain several times as much T_4CP as PCP, suggesting that it is prudent that measures be taken to minimize worker exposure to chlorophenols. Recommendations concerning such measures are summarized in the Appendix 2. Further, to assess the adequacy of the precautions taken, there is a clear need for reliable monitoring data for PCP levels in air, serum and urine. Monitoring of air must be continuous and associated with the individual. Information is also required on pulmonary and dermal absorption rates in man for the major commercial chlorophenols.

Table 9.A Levels of PCP in air and in serum and urine of occupationally exposed and non-occupationally exposed individuals

Activity	Workers Sampled (n)	Length of Exposure (years)	Levels of PCP in Air(mg/m^3) Mean (range)	Levels of PCP in Serum (mg/L) Mean (range)	Levels of PCP in Urine (mg/L) Mean (range)	Reference
Occupational Exposure						
Lumber, dipping	-	-	0.019(0.003-0.063)	--	2.83(0.12-9.68)	Arsenault, 1976
	18-22		--	3.78(0.15-17.4)	0.95(<0.01-7.80)	Klemmer *et al.*, 1980
Lumber, spraying	-	-	0.006(0.003-0.069)[1]	--	0.98(0.13-2.58)	Arsenault, 1976
		-	--	--	0.20(0.13-0.27)	Cranmer and Freal, 1970
Lumber, pressure treatment	-	-	0.014(0.004-1.000)[1]	--	1.24(0.17-5.57)	Arsenault, 1976
	23-24	-	--	1.72(0.02-7.70)	0.27(<0.01-2.40)	Klemmer *et al.*, 1980
	1	5	0.006(<0.001-0.015)	2.29(1.51-3.55)	0.30(0.09-0.76)	Wyllie *et al.*, 1975[3]
Lumber, carpentry	-	-	--	--	0.024(0.022-0.025)[2,5]	Cranmer and Freal, 1970
Lumber, office	1	10	0.002(<0.001-0.003)	0.65(0.42-0.75)	0.06(0.04-0.11)	Wyllie *et al.*, 1975[3]
Lumber, general	3	5(2-11)	0.001(<0.001-0.015)	1.11(0.35-3.00)	0.15(0.044-0.470)	Wyllie *et al.*, 1975[3]
Lumber and furniture employees	18	-	--	5.14 (0.43-14.0)	1.31(0.09-3.3)[5]	Begley *et al.*, 1977
Lumber workers exposed	24	-	--	--	0.12(0.033-0.301)[5]	Kalman and Horstman, 1983
Lumber, handle treated wood	3-5	-	5 ppb	0.71[5]	0.11[5]	Embree *et al.*, 1984
Lumber, other	3-5	-	6 ppb	0.24[5]	0.045[5]	Embree *et al.*, 1984
Lumber, control	5	-	--	0.058[5]	--	Embree *et al.*, 1984
Lumber mill, exposed workers	27	-	<0.0005	--	0.074(0.011-0.23)[5,6]	Kleinman *et al.*, 1986
Lumber mill, control (office, untreated wood)	22	-	--	--	0.030[5,6]	Kleinman *et al.*, 1986
Lumber, range of tasks	19	-	--	--	0.11(0.010-0.29)[5]	Currie and McDonald,1986
Pesticide, spraying	130	-	--	--	1.80(0.003-35.7)	Bevenue *et al.*, 1967
Mushroom cases, spray	8	-	--	--	0.092(N.D.-0.220)[4,5]	Chapman *et al.*, 1981
Mushroom cases, dip	37	-	--	--	0.115(N.D.-1.200)[5]	Chapman *et al.*, 1981
Hydro workers	32	-	--	--	0.004	Chapman *et al.*, 1981
Mushroom pickers	9	-	--	--	0.010(N.D.-0.023)	Chapman *et al.*, 1981
Textile workers	15	-	--	--	0.30(0.01-0.80)	Rappe *et al.*, 1982
Non-Occupational Exposure						
General population	117	-	--	--	0.04(N.D.-1.8)	Bevenue *et al.*, 1967
	32	-	--	0.3(0.02-7.20)[5]	0.03(<0.01-1.00)	Klemmer *et al.*, 1980
	6	-	--	--	0.005(0.002-0.011)[5]	Cranmer and Freal, 1970
	58	-	--	0.038(0.01-0.12)[5]	--	Morgade *et al.*, 1980
Chemist	1	-	--	0.048(0.038-0.068)	0.004(0.003-0.004)	Wyllie *et al.*, 1975[3]
Dutch draftees	99	-	--	0.128(<0.05-1.100)	--	Sangster *et al.*, 1982
Residents, treated houses	10	-	(0.0001-0.001)	(0.025-0.66)	(0.0007-0.015)	Sangster *et al.*, 1982
Autopsies, N. Bavaria	21	-	--	0.023[7] (0.005-0.069)	0.0044[7] (0.001-0.26)	Grimm *et al.*, 1981

1. Mean "average exposure levels" encountered by employees. Air at "maximum exposure" sites, next to sources, contained 0.026 mg/m^3 (lumber spraying sites) and 0.297 mg/m^3 pressure treatment site). 2. Range of replicate analyses of a single urine sample. 3. Mean concentrations shown are calculated from sampling data collected over a 5-month period. Mean air level for workers listed as "lumber, general", is calculated from data provided for all 11 sites over a 5-month period by Wyllie *et al.*, 1975. 4. N.D. = not detectable. 5. No correction made for density in converting ppb or ppm to mg/L. 6. Data from February 1982 used. 7. Median.

Table 9.B Levels of T_4CP in air and in serum and in urine of occupationally exposed and non-occupationally exposed individuals

Activity	Workers Sampled (n)	Levels of T_4CP in			Reference
		Air (mg/m^3) Mean (range)	Serum (mg/L) Mean (range)	Urine (mg/L) Mean (range)	
Occupational Exposure					
Lumber, prepare antisapstain solutions	7	0.066(0.005-0.21)	--	0.12(0.016-0.21)	Kauppinen and Lindroos, 1985[1]
Lumber, spraying or dipping	9	0.027(0.001-0.17)	--	0.078(0.014-0.23)	Kauppinen and Lindroos, 1985[1]
Lumber, machine stacking	16	0.075(0.033-0.12)	--	0.079(0.016-0.23)	Kauppinen and Lindroos, 1985[1]
Lumber, other	14	0.004 (0.001-0.010)	--	0.046(0.005-0.16)	Kauppinen and Lindroos, 1985[1]
Sawmill workers, dermal exposure	112	--	--	1.81(0.02-48.92)	Lindroos *et al.*, 1987[1]
Sawmill workers, respiratory exposure	34	--	--	0.21(0.02-3.09)	Lindroos *et al.*, 1987[1]
Sawmill workers, both dermal and respiratory exposure	84	--	--	0.32(0.02-11.09)	Lindroos *et al.*, 1987[1]
Lumber, handle treated wood	3-5	29 ppb	0.204[2]	0.125[2]	Embree *et al.*, 1984
Lumber, other	3-5	31 ppb	0.112[2]	0.093[2]	Embree *et al.*, 1984
Lumber, control	5	--	0.026[2]	--	Embree *et al.*, 1984
Lumbermill, exposed workers	27	0.004(0.001-0.011)[3]	--	0.15(0.007-0.45)[2,3]	Kleinman *et al.*, 1986
Lumbermill, control (office, untreated wood)	22	--	--	0.010[3]	Kleinman *et al.*, 1986
Lumber, range of tasks	19	0.033(<0.01-0.12)[4]	--	0.423(0.006-1.48)[5]	Currie and McDonald 1986
Lumber workers exposed	24	--	--	0.631(0.104-2.255)[2]	Kalman and Hortsman 1983
Lumber workers control	--	--	--	0.010[2]	Kalman and Hortsman 1983

1. Original results as µmol/L for all chlorophenols combined; tabled estimate assumes all CPs as T_4CP.
2. No correction made for density in converting ppb to mg/L.
3. Data from February 1982 used.
4. Total chlorophenols, roughly 2/3 of chlorophenols are T_4CP.

In addition, there appears to be little hazard from current levels of exposure to the microcontaminants in chlorophenate solutions. The maximum H_6CDD concentration reported in a recent survey of chlorophenate formulations from suppliers to Canada was 4 ppm (Agriculture Canada, 1987). Based on the maximum total urinary concentrations of T_4CP (1.479 mg/L) and PCP (0.293 mg/L) measured in a recent survey of Canadian sawmill workers (Currie and McDonald, 1986), maximum exposure to all chlorophenols is estimated at 35 µg per kg b.w. per day. Hence, the concurrent maximum exposure to H_6CDD contained in these chlorophenols is estimated to be 1.4×10^{-4} µg per kg b.w. per day for these workers. This exposure is approximately 3 orders of magnitude below the lowest NOAELs for a range of endpoints in the mouse and rat exposed to H_6CDD isomers (Table 8). It is likely that toxic responses to the chlorophenols themselves would be observed before any effects to H_6CDD were expressed. However, these calculations and those of Williams (1982) and Arsenault (1976) should not be used to justify the marketing of chlorophenols with high levels of microcontaminants. There remains the potential for bioaccumulation of these chemicals in the environment and in human tissue, and in view of the known carcinogenicity of H_6CDD, the microcontaminant content of PCP should be kept as low as is feasible.

It is worth noting that past exposures in the workplace were likely higher than those reported by Currie and McDonald (1986) as were the concentrations of microcontaminants. Thus, past exposures are likely to have posed a greater risk to health than present exposures.

b) Conclusion

The major area of occupational-health concern for the use of chlorophenols in Canada is the lumber industry and focuses on PCP and T_4CP. There is little doubt that PCP, T_4CP, and their sodium salts are toxic materials that have caused significant discomfort for exposed workers. Potentially the most deleterious short-term effect of PCP and T_4CP exposure is on the fetus (Chapter E) and therefore pregnant women should avoid contact with these chlorophenols or with materials treated with them. An elevated incidence of cancer in Canadian woodworkers exposed to PCP and T_4CP is currently under investigation in an NHW-sponsored study, although the present limited evidence suggests that PCP is not carcinogenic in animals (Chapter E.6). There is evidence of neurological disorders, and effects on some organs and the immune system in some exposed workers. Further, it is likely that the recommended ADI of 3 µg/kg bw/day for PCP is often exceeded at present occupational exposure-levels.

There is therefore a clear requirement for a reduction in occupational exposure to PCP and T_4CP. (Little is known about the toxic properties of the other chlorophenols, but these are no longer registered for use in Canada.) Emphasis must be placed on reducing levels of PCP and T_4CP within or near wood-treatment facilities, and the potential for dermal contact. Improvements in industrial hygiene can cause significant reductions in urinary PCP levels. Voluntary guidelines for the proper use of chlorophenols and their salts in the lumber and wood preserving industry have been prepared by a Canadian Federal Provincial Industry task force in British Columbia and should be followed by those individuals using these chemicals (Konasewich and Henning, 1988a,b, Konasewich *et al.*, 1983). The guidelines are designed to reduce industrial exposure and environmental contamination from PCP, T_4CP and their sodium salts at sites of use by careful design of wood treatment facilities and operating procedures. The health-based guidelines are outlined in general terms in Appendix 2; readers requiring more detail are referred to the Codes of Good Practice themselves.

No clear-cut relationship has been established between the levels of chlorophenols in air and human urine. Calculations based on workplace residue measurements suggest that some previous estimates of occupational chlorophenol absorption and body burdens may seriously underestimate worker exposure by ignoring dermal uptake. Continuous, individual biological monitoring would be needed to monitor the adequacy of industrial hygiene measures, and to provide adequate exposure data to alert the responsible agency to potentially hazardous exposures where they exist. There is also a need to determine the absorption rates for PCP and T_4CP in human lungs and on human skin.

Microcontaminants in recent commercial mixtures of chlorophenols are now at relatively low concentrations (ppm). The most hazardous microcontaminant of PCP and T_4CP is H_6CDD; however, the toxic effects of subchronic exposure to this compound in present-day technical chlorophenols are unlikely to be expressed before significant toxicity due to PCP or T_4CP is observed. The remaining potential hazard posed by the presence of H_6CDD in PCP rests with its accumulation in human tissues, especially liver and fat, combined with its known carcinogenicity to animals. Storage and mobilization of lipid-associated H_6CDD may pose a long-term health hazard. In light of this potential, reductions in the concentrations of microcontaminants to the lowest levels feasible is advisable in order to lower overall exposure to the chlorinated dibenzo-p-dioxins and furans.

There is currently no health-based justification for a ban on the use of PCP or T_4CP or their salts. From a health perspective, further reductions in the use of these chemicals, in their microcontaminant contents or in the potential for worker exposure would be justified on the basis of the existing toxicologic and epidemiologic information. A careful retrospective analysis of vital statistics on woodworkers in relation to chlorophenol exposure in Canada is currently under way in a study initiated with resources provided by NHW (Herzman, C., and Gallagher, R., Department of Health Care and Epidemiology, University of B.C. "Retrospective cohort study of B.C. sawmill workers exposed to chlorophenates").

Table 10. Exposure and excretion calculations for lumber mill workers in the USA[1]

Job Title	Total PCP (mg)			Ratios		
	Air[2] (A) Mean (range)	Serum[3] (S) Mean (range)	Urine[4] (U) Mean (range)	A/S	A/U	S/U
Oregon						
Dipper	0.27 (0.04-0.91)	--	3.96 (0.17-13.55)	--	.07	--
Sprayer	0.09 (0.04-0.99)	--	1.37 (0.18-3.61)	--	.07	--
Pressure Treater	0.20 (0.06-14.4)	--	1.74 (0.24-7.80)	--	.11	--
Idaho						
Pressure Treater	0.09 (<0.01-0.22)	6.18 (4.08-9.59)	0.42 (0.13-1.06)	.014	.21	15
General, Yard	0.01 (<0.01-0.22)	3.00 (0.95-8.10)	0.21 (0.06-0.66)	.003	.05	14
Office Manager	0.02 (<0.01-0.03)[5]	1.76 (1.13-2.03)	0.08 (0.06-0.15)	.011	.25	22

1. Oregon (Arsenault, 1976) and Idaho (Wyllie *et al.*, 1975).
2. Based on 14.4 m^3/8h shift of "moderately heavy" work (Kozak *et al.*, 1979).
3. Based on 45 mL plasma/kg and a 60 kg person (Altman and Dittmer, 1961).
4. Based on 1.4 L urine/day per person (Kozak *et al.*, 1979).
5. Based on 9.6 m^3/8h shift of "light activity" (Snyder, 1974).

3. Non-Occupational Exposure

a) Considerations

Non-occupational exposure to chlorophenols may include exposure to ambient levels of these chemicals in air and water, and exposure to chlorophenols in food, drugs and consumer products. The widespread use of chlorophenols has resulted in low-level contamination of nearly every environmental compartment. Levels of PCP have been detected at ppb concentrations in serum, urine, adipose tissue, organs and even seminal fluid of individuals used as non-occupationally exposed control groups (Williams *et al.*, 1984; Sangster *et al.*, 1982; Grimm *et al.*, 1981; Kuehl and Dougherty, 1980; Morgade *et al.*, 1980; Klemmer *et al.*, 1980; Kozak *et al.*, 1979; Arsenault, 1976; Shafik, 1973; Bevenue *et al.*, 1967). Organs and some tissues may in some instances be characterized by higher (ppm) concentrations (Grimm *et al.*, 1986).

Sources of chlorophenols to the Canadian environment have been discussed by Jones (1981, 1984). Major routes of entry include wood-preserving and wood-protection plants, and domestic or industrial treatment of wood or other products already in service; minor sources include loss of petrochemical drilling fluids containing PCP, chlorination of raw water supplies, incineration of industrial and municipal wastes and miscellaneous waste emissions of industry. Accidental spillage of chlorophenols has not been measured but has resulted in environmental damage (Jones, 1981).

(i) Air

There are no Canadian data available on levels of chlorophenols in ambient air. Data from other developed countries indicate that levels of PCP in the air at large are exceedingly low, i.e. up to 7.8 ng/m^3 (Cautreels *et al.*, 1977). There is not likely to be any health hazard associated with airborne levels that are five orders of magnitude less than the current TLV$^{(R)}$ of 0.5 mg/m^3.

High concentrations of PCP in indoor air of homes built with pressure treated lumber or painted with PCP-based wood preservatives have led to symptoms of PCP toxicity and elevated levels of PCP in serum and urine (Table 11). Nausea, vomiting and dermatological lesions have been reported in several families exposed to PCP and its solvent carriers (Sangster *et al.*, 1982). Indoor air levels of PCP in winter are up to 100 times higher (50-100 µg/m^3) than in summer primarily because of reduced ventilation and changes in humidity and temperature (Gebefügi *et al.*, 1979). Mean PCP levels in indoor air samples collected from PCP-treated log homes in summer months are roughly two orders of magnitude lower than those reported in air at lumber mills (Tables 9 and 11).

Calculations of total PCP exposure from airborne levels found in PCP-treated homes, based on 23.8 m^3 air inhaled/day per adult (Snyder, 1974), indicate that excretion of PCP, based on 1.4 L urine/day per adult, is 2-30 times greater than the estimated total inhalation exposure. Only the data of Sangster *et al.* (1982) demonstrate a 1:1 relationship between exposure and excretion. The data provided in Table 11 once again point to the need for accurate, constant, individual air-monitoring, information on the contribution of dermal uptake to total exposure, and data on the recent previous exposure of individuals to PCP.

The extensive use of chlorophenols on interior wood surfaces may cause discomfort and should be avoided. For wood homes already treated with PCP or T_4CP, painting with a clear sealer such as varnish or urethane may markedly reduce airborne concentrations of PCP (Dementi, 1980; Levin and Hahn, 1986). Wax sealers have also been used. Heating a

Table 11. Levels of PCP in air and in urine and plasma of residents of treated log homes

Sample Size (n)		PCP Levels in			
Homes	Subjects	Indoor Air ($\mu g/m^3$)	Plasma (mg/L)	Urine (mg/L)	Reference
PCP Treated Homes					
11	32	--	0.330 (0.116-1.084)	0.013 (0.002-0.087)	Ing, 1981
1	5	0.20-0.38	0.580-1.750	0.047-0.216	Hernandez and Strassman-Sundy, 1980.
1	2	0.769	0.227-0.319	0.025-0.095	USEPA, 1981b
1	6	0.14-1.2	0.025-0.190	0.0018-0.008	Sangster *et al.*, 1982
Control					
N.S.[a]	11	--	0.048 (0.015-0.055)	0.003 (0.001-0.008)	Ing, 1981
1[b]	2	--	0.034-0.075	1.4(0.001-0.002)	Ing, 1981

a. not specified

b. residents of untreated log homes

well-ventilated building over a prolonged period can eventually reduce PCP levels in household air significantly (Sangster *et al.*, 1982; Levin and Hahn, 1986).

Nonoccupational exposure to chlorophenols via inhalation is likely to be quite low. The indoor air of homes not treated with PCP contains less than 0.1 µg PCP/m^3 (WHO, 1987). Outdoor air has been reported to contain as much as 0.0078 µg PCP/m^3 (Cautreels *et al.*, 1977). Assuming that a person inhales 23.8 m^3 of air per day (Snyder, 1974), that this volume is a 4:1 mix of indoor and outdoor air, and that 100% of the inhaled PCP is absorbed, then this individual would take up 1.9 µg per day via inhalation.

(ii) Water

There are limited data on chlorophenol levels in water. In most cases the data listed in the literature are not part of a general survey but incidental measurements (e.g. to determine the origin of fish kills), or for the purpose of modelling the dispersal of chlorophenols in the environment. Levels of PCP in a survey of Great Lakes water ranged from undetectable to 1.7 ppb. The highest levels were along Lake Erie near Windsor and Lake Ontario near Picton (Fox, 1978 in Jones, 1981). Snow-pack samples in Ontario have also been shown to contain up to 3 parts per trillion of PCP and demonstrate the potential for aerial transport of chlorophenols. In general, levels of chlorophenols in ambient Canadian waters rarely exceed 2 µg/L.

The chlorophenols in raw water are mainly due to industrial discharges of chlorophenolic materials. However, there is recent evidence that the chlorophenols found in finished drinking water may be derived in part from naturally-occurring phenolic acids found in ground and surface waters (Pierce, 1978a). Sithole and Williams (1986) reported that low levels of a variety of chlorophenols occurred infrequently in potable waters at 40 Canadian treatment plants. Chlorination increased the concentrations of 2-MCP (maximum observed: 65 ng/L), 4-MCP (127 ng/L), 2,4-DCP (72 ng/L), 2,6-DCP (33 ng/L), and 2,4,6-T_3CP (719 ng/L), but decreased those of 2,3,4,5-T_4CP (completely eliminated) and PCP (34 ng/L).

The Canadian recommendation for a Maximum Acceptable Concentration (MAC) for phenolic compounds in water is 2 µg/L (NHW, 1980) and is based on the objectionable taste and odour of these substances. There is no health hazard associated with the intake of or exposure to drinking water containing 2 ppb chlorophenols, which is far in excess of any concentrations reported in Canadian drinking waters (Sithole and Williams, 1986). Based on a consumption of 1.4 L/day of water (NHW, 1981) containing 2 µg/L of PCP, a 70 kg person would ingest a maximum of 0.04 µg/kg per day. This value is approximately 5 orders of magnitude below the no-effect-level for fetotoxicity in pregnant mammals exposed to PCP during gestation and the no-effect-level established in chronic lab animal feeding studies.

(iii) Food

Levels of chlorophenols in Canadian foods are generally low and unlikely to pose any significant threat to the health of Canadians. A survey of T_4CP and PCP in vegetables and milk in Alberta indicated mean levels below 0.1 ppm, with most foodstuffs characterized by low ppb concentrations (Currie, 1978, in Jones, 1981). Occasional levels above 1 ppm were as- sociated with the storage of the food commodity in a PCP-treated wooden bin. Survey data from the United States report that mean concentrations in grains and cereals, sugar products and fruit are in the low µg/kg range (Johnson and Manske, 1977). More recently, Graham (1982) has examined PCP levels in a wide range of meat products from across Canada (Table 12). Fifty percent of the 150 meat specimens analysed in 1979-1980 were found to contain PCP residues. Of those containing PCP, 60% had <0.02 ppm and only 4% (all pork products) had >0.1 ppm. The following year 45% of the meats contained PCP and 7% of those containing PCP residues

had >0.1 ppm (pork products and poultry). Other surveys of chlorophenol residues in pork and poultry fat and liver (Neidert *et al.*, 1984; Ryan *et al.*, 1985) have also reported widespread contamination of Canadian products. Comparison of their data suggests that the incidence of such contamination has decreased since the restrictions on registered PCP uses outlined in Section 3(a(vi)) of this chapter.

The major source of the PCP and T_4CP found in vegetables and meat products appears to be chlorophenol-treated wood (Jones, 1981). Use of PCP-treated lumber in farm buildings and the use of wood shavings from PCP-treated lumber has resulted in tainted meat products in Canada and the USA. Suspensions of PCP products registered for use on food containers and the interior of farm buildings in Canada has reduced this exposure since 1981 (Chapter F.3(a)(vi)). Accidental contamination of products during transport has also been reported (Jones, 1981). Use of PCP in the hide-tanning industry has resulted in elevated levels of this chlorophenol in some gelatin products; gelatin is a byproduct of tannery operations (Stijve, 1981). Fat scrapings from hides treated with PCP are used to supplement animal feeds, and may cause chick edema disease, as well as accumulations of the chlorophenol and its impurities in animal tissues

Fish also contain detectable levels of PCP. Zitko *et al.* (1974) reported levels of <1 to 4 ppb in a variety of marine fish from the east coast of Canada. Strachan (Jones, 1981) reported as much as 1.0 ppm of PCP in lake trout from Lake Superior sites adjacent to wood industry facilities. Aquatic animals appear to be one of the few groups to accumulate PCP (Chapter D.2(c)).

Table 12. Concentrations of PCP in Canadian meat and meat products[1]

Date	Commodity	Samples Analyzed (n)	Samples with Detectable Residues (n)	Samples with Residues >0.1 ppm (n)	Range of Residues (ppm)
1979-1980	**Beef** - liver	11	6	0	0.01-0.058
	- fat	10	1	0	<0.039
	- corned beef, baloney, hamburger	31	13		0.01-0.034
	Pork - liver	10	9	2	0.01-0.170
	- kidney	8	6	0	0.01-0.098
	- bacon, sausage, chops	30	13	1	0.01-0.43
	Poultry - liver	10	2	0	0.01-0.049
	- whole chicken	20	17	0	0.01-0.049
	Processed Meats				
	- poultry (rolls, loaves)	10	5	0	<0.019
	- pork (blood sausage)	10	3	0	<0.019
	TOTAL	150	75	3	
1980-1981	**Beef** - gelatin	8	0	0	<0.01
	Pork - fat	17	11	0	0.01-0.061
	- liver	2	2	2	0.19-0.315
	Poultry - fat	72	35	0	0.01-0.10
	- liver	28	9	2	0.02-0.15
	TOTAL	127	57	4	

1. Graham, 1982.

Levels of chlorophenols in total diet have not been estimated in Canada. Estimates in the USA range from 0 to 6.0 µg/day per person (NRCC, 1982). The reported levels of PCP in Canadian foods indicate that average daily diets are unlikely to contain more than the estimated US maximum of 6 µg/day. Based on this intake of PCP per day there is no potential health threat for an average 70 kg person, since 0.09 µg/kg per day is four orders of magnitude below the no-effect-level in any mammalian toxicity study with PCP. Individuals consuming fish from localized areas with high chlorophenol inputs could ingest somewhat higher levels than this (e.g. 1000 µg/kg of PCP * 0.14 kg/day of fish for a 70 kg person = 2 µg/kg b.w. per day), which are still roughly 1000 times less than NOAELs determined in animal studies.

Concern has been expressed over the presence of H_6CDD and other microcontaminants in meat and fish. The chlorinated dibenzo-p-dioxins and furans are lipophilic and accumulate in animal tissue. Gelatin products made from cow hides which were treated with PCP can contain high levels of chlorinated dioxins (Ahlborg and Thunberg, 1980). Health and Welfare Canada has set standards for the maximum allowable dioxin content of foods for sale in Canada under the Food and Drugs Act (NHW, 1982), as follows:

> "B.01.046. (1) A food is adulterated if any of the following substances or classes of substances are present therein or have been added thereto:
> (p) chlorinated dibenzo-p-dioxins.
>
> B.01.047. Notwithstanding section B.01.046.
> (f) fish is not adulterated by reason only that it contains 20 parts per trillion or less of 2,3,7,8-tetrachlorodibenzoparadioxin".

(iv) Miscellaneous Sources

A wide range of miscellaneous sources contribute to human nonoccupational exposure to chlorophenols. Many veterinary and disinfectant products in Canada contain chlorophenols. In addition photographic solutions, fabrics, and some home-care products and pharmaceuticals can include these compounds. The presence of PCP and T_4CP on treated wood products and in the soil surrounding pressure-treated wood structures could cause low-level exposure in the general population and especially small children. Hobbyists working with treated lumber may also be exposed for short periods to chlorophenols via dermal absorption and via inhalation of PCP-impregnated saw dust.

Quantitative assessment of the exposure likely to result from these activities is difficult.

(v) Overall Ambient Exposure

The paucity of data on levels of exposure of Canadians to chlorophenols makes overall estimates of exposure difficult. A conservative estimate of overall ambient exposure follows for an average 70 kg adult not occupationally exposed to chlorophenols and not living in a home extensively treated with chlorophenol wood preservatives:

6 µg/day in food
2.8 µg/day in water
1.9 µg/day in air
2.0 µg/day miscellaneous exposure
12.7 µg/day Total = 0.18 µg/kg b.w. for a 70 kg adult.

Even if this intake was inflated by consuming highly contaminated fish, as in the earlier example, this exposure (approximately 2 µg/kg b.w. per day) would still be lower than the ADI calculated by the National Academy of Sciences (1977) and unlikely to adversely affect human health.

Levels of PCP in most non-occupationally exposed persons probably reflect exposure to chlorophenols in food, water, indoor air, disinfectants, drugs, cosmetics and other surreptitious sources. Levels of PCP in adipose tissue have averaged 23 to 25 ppb in the general population (Morgade *et al.*, 1980; Shafik, 1973). Higher levels (140 ppb) have been reported in some Japanese (Ohe, 1979), and in human seminal fluid (100-200 ppb, Keuhl and Dougherty, 1980). The reported mean levels of PCP in serum from the general population range between 23 and 320 ppb and in urine between 3 and 40 ppb (Tables 9 and 11).

(vi) Current Regulations

Agriculture Canada has repeatedly proposed or announced changes in the regulatory status of chlorophenols (Agriculture Canada, 1980, 1987). Based on potential occupational, bystander, human and animal health hazards that may be associated with certain registered uses of chlorophenol products, Agriculture Canada provided the following revisions to their standards for use effective January 1, 1981.

- Suspension of chlorophenol products carrying label instructions for use as wood preservatives and/or wood stains for interior home use;
- Suspension of products containing sodium pentachlorophenate for use as fungicides in mushroom houses and on tools for mushroom culture;
- Suspension of products containing PCP for use as wood preservatives on wooden food containers and on horticultural lumber, e.g. seed flats, stakes, greenhouse lumber, etc.;
- Suspension of products containing PCP and carrying label instructions for use as wood preservatives on above-ground interior woodwork of farm buildings, e.g. dry locations such as walls, floors, bins, feed troughs, silos, stalls, chicken roosts, etc. (Agriculture Canada has recommended that PCP-treated wood be used on the farm only where the wood is in ground contact, e.g. fence posts, support poles, foundation supports, and the bottom six inches of stall skirt boards);
- Suspension of all chlorophenol products carrying label instructions for use as microbiocides in curing hides;
- Suspension of products labelled for use as herbicides and soil sterilants, except those labelled for destruction of moss on roofs;

- Suspension of products containing the chlorophenols and their sodium salts for use as slimicides in pulp and paper mill operations;
- Suspension of all domestic class products for application by spray methods.

In addition Agriculture Canada imposed a limitation via product labels on the incorporation of chlorophenols into materials "of which the end use will result in prolonged direct skin contact e.g. life jackets, sleeping bags, sports equipment."

The regulatory status of penta- and tetrachlorophenol products (lower chlorinated phenols are not registered for use in Canada at present) is currently under review. Background and regulatory options are presented in the Discussion Document released recently by Agriculture Canada (1987).

As of October 1986, there are 122 products registered for use in Canada which contain PCP, T_4CP, or their salts; 96 are commercial and/or manufacturing products and 26 are domestic (Ranger, 1986).

b) Conclusion

Levels of exposure to chlorophenols in the ambient environment are poorly documented. Levels of chlorophenols in air are unlikely to be above 10 ng/m^3; however, there are no Canadian data. The presence of PCP in snow indicates that aerial transport exists.

Indoor air of PCP treated homes usually contains less than 1 µg/m^3 of PCP (Table 11) and can cause symptoms of PCP intoxication similar to those reported by occupationally exposed persons. Estimates are that adults have been exposed to as much as 40 µg PCP/day in such homes. Recent suspensions of registered uses of chlorophenols in domestic aerosol products and as indoor wood preservatives should be effective in reducing the potential for high indoor air levels of PCP in Canadian homes.

Levels in water are rarely reported to exceed 2 µg/L, the current MAC for Canadian drinking water. Restrictions on the use of PCP as a slimicide in pulp and paper mills will help reduce ambient water levels in some areas. Lower chlorinated phenols can be produced in minute quantities during raw water chlorination. Low levels are readily detected by taste and odour.

Canadian foods contain low levels of PCP and T_4CP (≤5 µg/kg) although certain products of the tanning industry (gelatin), some pork and poultry products from animals exposed to PCP-contaminated wood shavings and some vegetables stored in PCP-treated bins have shown higher concentrations. No food-basket survey to measure chlorophenol levels in food sources has been undertaken in Canada; however, total intake is unlikely to exceed estimated USA maximum intakes of 6 µg/day, except for certain localized populations consuming much highly-contaminated fish, who may have intakes one to two orders of magnitude higher than this. Recent restrictions on the use of chlorophenols on farms, in soil, in food containers and in the tanning and pulp and paper industries are likely to be effective in reducing exposure of Canadians to chlorophenols in food.

Miscellaneous exposures to chlorophenols are difficult to quantitate; however, the opportunity exists for both dermal and oral exposure in infants and young children playing on, or in the vicinity of treated wood products, or on floors treated with disinfectants containing chlorophenols. Adult exposure is likely restricted to the use of products containing chlorophenols such as disinfectants, pharmaceuticals, cosmetics and treated wood.

The overall health hazard associated with non-occupational exposures to chlorophenols is not known but likely to be extremely low. A conservative estimate of total chlorophenol exposure is 12.7 µg/day per adult. Daily exposure of a 70 kg person to this amount of PCP, the most common and toxic chlorophenol, is equivalent to 0.18 µg/kg per day. This level of exposure is 10 000 times less than the lowest no-adverse-effect-level reported in lab animal studies (Table 7), suggesting that present levels of nonoccupational exposure to chlorophenols pose no significant hazard.

However, given the limited prospects for risk management in the use of domestic chlorophenol-based wood preservatives (and the resultant potential for use of such products contrary to label instructions), and the availability of alternative chemicals to satisfy the small market for them, consideration should be given to suspending the Canadian registration for all domestic class wood-preservation products containing pentachlorophenol and related chlorophenols and their salts.

Efforts should be made to ensure that all microcontaminants in commercial chlorophenols are at their lowest possible levels. Chlorinated dibenzo-p-dioxins and furans have been found to accumulate in the food chain, and one congener is carcinogenic to rats and mice (Chapter E.7(a)). Furthermore, the decision to incinerate wastes containing chlorophenols should be carefully weighed because of the potential for the generation of additional PCDDs and PCDFs.

Appendix 1

Agriculture Canada
Pesticides Directorate
Label Improvement Program (L.I.P.)
November 25, 1985

Canadian Federal Labelling Requirements for Pest Control Products Containing Pentachlorophenol/Tetrachlorophenol and Related Salts.

Group A:

All registrations of solutions (SN) and emulsifiable concentrates (EC) in the RESTRICTED (R) or COMMERCIAL class (C) containing 17% pentachlorophenol and/or related chlorophenols, other active ingredients and petroleum distillates.

The following should appear on all such Restricted or Commercial (Group A) labels:

1. The DANGER POISON sign, symbol and signal words. Other precautionary signs, symbols and statements should remain on the label.
2. The words "READ LABEL BEFORE USING" in bold capital letters.
3. The words "KEEP OUT OF REACH OF CHILDREN" in capital bold letters.
4. The words "FOR EXTERIOR USE ONLY" "NOT FOR USE IN DWELLINGS" in *bold* capital letters.
5. DIRECTIONS FOR USE:

   Use limitations regarding indoor use and application to surfaces that may contact food or animal feed, or for picnic tables, benches, chairs, playground structures or wood which may come into prolonged contact with humans, animals or living plants should be placed under the directions for use. See Appendix 1A for the appropriate directions for use limitations for each use pattern described on the label.
6. It appears that some formulations may pose a fire hazard. Based on the PCP Guidelines each registrant should determine whether their product needs a flammability sign, symbol and signal word on the label based on the flash point and combustability of their product.

   Any Commercial classification, high concentration petroleum distillate product requires: "Product contains Petroleum Distillate. Do not store, pour or use near open flame."
7. PRECAUTIONS:

   May be fatal if swallowed, inhaled or absorbed through the skin. Causes skin and eye irritation. Do not get on skin or clothing or in eyes. Do not breathe vapours or spray mist. Wear impermeable clothing and footwear and synthetic rubber gloves when handling concentrates or freshly treated wood and during treatment. Use only under well ventilated conditions. Wear eye goggles or face shield when mixing and applying. Wash thoroughly with soap and water after using the product. Toxic to fish, plant life

and animals. Keep away from foodstuff, children, pets and livestock. Close container when not in use. Keep away from heat, open flame and sparks during storage or use. DO NOT STORE IN DWELLINGS.

8. FIRST AID:

   IF IN EYES, flush eyes with water for 5 minutes and get medical attention.

   IF ON SKIN, remove contaminated clothing and wash skin and hair immediately with soap and water. Wash contaminated clothing before reuse, *separately from other laundry*.

   IF SWALLOWED, DO NOT INDUCE VOMITING, rush to nearest hospital taking label with you or phone doctor or Poison Control Centre. Administer artificial respiration if not breathing.

9. TOXICOLOGICAL INFORMATION:

   Contains PETROLEUM DISTILLATE. Active ingredient is a metabolic stimulant and causes hyperthermia. Treat symptomatically. Chemical burns can result from eye contact or prolonged skin contact.

10. DISPOSAL:

    Follow provincial instructions for any required additional cleaning of the container prior to its disposal or reconditioning.

    Dispose of the container in accordance with provincial requirements.

    For information on the disposal of unused unwanted product and the cleanup of spills contact the regional office the Environmental Protection Service, Environment Canada.

    For small spills. Recover free liquid. Soak up residue with solids absorbent. DO NOT FLUSH INTO SURFACE STREAMS. INFORM ENVIRONMENT CANADA.

11. Notice to user must be included on the label.

Group B:

All registrations of ready-to-use COMMERCIAL class (C) solutions (SN) containing 5% pentachlorophenol and/or related chlorophenols and petroleum distillates.

The following should appear on all Commercial (Group B) labels:

1. The DANGER POISON sign, symbol and signal words.
2. The words "READ LABEL BEFORE USING" in bold capital letters.
3. The words "KEEP OUT OF REACH OF CHILDREN" in bold capital letters.
4. The words "FOR EXTERIOR USE ONLY" "NOT FOR USE IN DWELLINGS" in bold capital letters.
5. DIRECTIONS FOR USE:

   Use limitations regarding indoor use and application to surfaces that may contact food or animal feed, picnic tables, benches, chairs, playground structures or wood which may come into prolonged contact with humans, animals or living plants should be placed under the *directions for use*, along with appropriate use procedures for product types. See Appendix 1A, Section I.

6. It appears that some of these formulations may pose a fire hazard. Based on the PCP Guidelines each registrant should determine whether their product needs a flammable sign, symbol and signal word on the label based on the flash point and combustability of their product.

   Any Commercial classification, high concentration petroleum distillate product requires: "Product contains Petroleum Distillate. Do not store, pour or use near open flame."

7. PRECAUTIONS:

   May be harmful or fatal if swallowed, inhaled or absorbed through the skin. Causes skin and eye irritation. Avoid contact with skin, clothing and eyes. Avoid breathing vapours or mist. Use only under well ventilated conditions. Wear impermeable clothing and footwear and synthetic rubber gloves when handling concentrate, or freshly treated wood and during treatment. Wear eye goggles or face shield when applying. Wash thoroughly with soap and water after use. Toxic to fish, plant life and animals. Close container when not in use. Keep away from heat, open flame and sparks. DO NOT STORE IN DWELLINGS. Do not burn treated wood waste in domestic stoves or fireplaces.

8. FIRST AID:

   IF IN EYES, flush with water for 5 minutes and get medical attention.

   IF ON SKIN, remove contaminated clothing and wash skin and hair immediately with soap and water. Wash contaminated clothing before reuse, *separately from other laundry*.

   IF SWALLOWED, DO NOT INDUCE VOMITING, rush to nearest hospital taking label with you or phone doctor or Poison Control Centre.

9. TOXICOLOGICAL INFORMATION:

   Contains PETROLEUM DISTILLATES. Product is a metabolic stimulant and causes hyperthermia. Treat symptomatically. Chemical burns can result from eye contact or prolonged skin contact.

10. DISPOSAL:

    1. Follow provincial instructions for any required additional cleaning of the container prior to its disposal or reconditioning.
    2. Dispose of the container in accordance with provincial requirements.
    3. For information on the disposal of unused, unwanted product and the cleanup of spills contact the regional office of the Environmental Protection Service, Environment Canada.

4. For small spills. Recover free liquid. Soak up residue with solids absorbent. DO NOT FLUSH INTO SURFACE STREAMS. INFORM ENVIRONMENT CANADA AS IN # 3.

11. Notice to user must be included on the label.

Group C:

All registrations of ready-to-use DOMESTIC (D) class solutions (SN) containing 5% pentachlorophenol and/or related chlorophenols and petroleum distillates.

The following should appear on all such DOMESTIC (Group C) labels:

1. The DANGER POISON sign, symbol and signal words are required on the DOMESTIC label for a product containing more than 10% petroleum distillate.
2. The words "READ LABEL BEFORE USING" in bold capital letters.
3. The words "KEEP OUT OF REACH OF CHILDREN" in bold capital letters.
4. The words "FOR EXTERIOR USE ONLY" "NOT FOR USE IN DWELLINGS" in bold capital letters. Implied indoor or enclosed area uses of products should be deleted.
5. Use limitations regarding indoor use and application to surfaces that may contact food or animal feed, picnic tables, benches, chairs, playground structures or wood which may contact humans, animals or living plants for prolonged periods should be placed under the directions for use, along with appropriate use procedures for the product types described in Appendix 1A, Section II.

6 It appears that these formulations may pose a fire hazard. Based on the PCP Guidelines each registrant should determine whether their product needs a flammable sign, symbol and signal word on the label, based on the flash point and combustability of their product.

Any Commercial classification, high concentration petroleum distillate product requires: "Product contains Petroleum Distillate. Do not store, pour or use near open flame."

7. PRECAUTIONS:

May be harmful or fatal if swallowed, inhaled or absorbed through the skin. May cause skin and eye irritation. Avoid contact with skin, clothing and eyes. Avoid breathing vapours. Use only under well ventilated conditions. Do not apply by spray or dip methods. Wear synthetic rubber gloves when treating or handling freshly treated lumber. Wash thoroughly with soap and water after use. Toxic to fish, plant life and animals. Close container when not in use. DO NOT STORE IN DWELLINGS. Keep away from heat, flames and sparks. Do not burn treated wood.

8. FIRST AID:

IF IN EYES, flush eyes with water for 5 minutes and get medical attention.

IF ON SKIN, remove contaminated clothing and wash skin and hair immediately with soap and water. Wash clothing before reuse, *separately from other laundry*.

IF SWALLOWED, DO NOT INDUCE VOMITING, rush to nearest hospital taking label with you, or phone doctor or Poison Control Centre.

9. TOXICOLOGICAL INFORMATION:

Contains PETROLEUM DISTILLATES. Active ingredient is a metabolic stimulant and causes hyperthermia. Treat symptomatically. Chemical burns can result from eye contact or prolonged skin contact.

10. DISPOSAL:

Do not reuse empty containers. Discard empty containers and unused portions of treated wood in trash for burial at approved landfill sites.

11. Notice to user must be included on the label.

Group D1

All registrations of ready-to-use COMMERCIAL class pastes (PA) and solutions (SN) containing 9-15% pentachlorophenol and/or related chlorophenols and other active ingredients.

The following should appear on all such COMMERCIAL (Group D1) labels:

1. The WARNING POISON sign, symbol and signal words on products containing only PCP and the DANGER POISON on products containing pentachlorophenol in combination with other active ingredients.
2. The words "READ LABEL BEFORE USING" "EXTERIOR USE ONLY", "NOT FOR USE IN DWELLINGS" in bold letters.
3. The words "KEEP OUT OF REACH OF CHILDREN" in bold letters.
4. The precautions regarding protection of farm animals from treated poles should be put under the instructions for use.

Special instructions regarding the maintenance or cleaning of specialized equipment used to apply paste formulations should be included under appropriate *directions for use*. See Appendix 1A, section III for applicable use precautions and limitations.

5. It appears that these formulations may pose a fire hazard. Based on the PCP Guidelines each registrant should determine whether their product needs a flammable sign, symbol and signal word on the label, based on the flash point and combustability of their product.

Any Commercial classification, high concentration petroleum distillate product requires: "Product contains Petroleum Distillate. Do not store, pour or use near open flame."

6. PRECAUTIONS:

May be harmful if swallowed, inhaled or absorbed through the skin. Causes skin and eye irritation. Do not get on skin,

clothing or in eyes. Avoid breathing vapours. Wear goggles or face shield when handling. Wash thoroughly with soap and water after using the product. Wear elbow length gloves impervious to the treatment formulation. Wear protective clothing, long sleeved shirts, pants, boots, hat and apron impervious to the wood treatment formulation. Avoid skin contact. Wash thoroughly after skin contact and before eating, drinking, use of tobacco products, or using restrooms. Change protective clothing when it shows signs of contamination. Launder work clothing separately from other household items. This product is toxic to fish, plant life and animals.

7. FIRST AID:

   IF IN EYES, flush eyes with water for 5 minutes and get medical attention.

   IF ON SKIN, wash skin and hair immediately with soap and water, remove contaminated clothing and *wash separately from other laundry.*

   IF SWALLOWED, DO NOT INDUCE VOMITING, rush to nearest hospital taking label with you, or phone doctor or Poison Control Centre.

8. TOXICOLOGICAL INFORMATION:

   Contains PETROLEUM DISTILLATE. Active ingredient is a metabolic stimulant and causes hyperthermia. Treat symptomatically. Chemical burns can result from eye contact or prolonged skin contact.

9. DISPOSAL:

   Follow provincial instructions for any required additional cleaning of the container prior to its disposal or reconditioning.

   Dispose of the container in accordance with provincial requirements.

   For information on the disposal of unused, unwanted product and the cleanup of spills contact the regional office the Environmental Protection Service, Environment Canada.

   For small spills. Recover free liquid. Soak up residue with solids absorbent. DO NOT FLUSH INTO SURFACE STREAMS. INFORM ENVIRONMENT CANADA AS IN # 3.

10. Notice to user must be included on the label.

Group D2

A ready-to-use COMMERCIAL (C) solution for impregnated fabric (IF) containing chlorophenates and other active ingredients.

The following should appear on all such Commercial (Group D2) labels for such products:

1. The DANGER POISON sign, symbol and signal word.
2. The words "READ LABEL BEFORE USING" in bold letters.
3. The words "EXTERIOR USE ONLY", "NOT FOR DWELLINGS" and "KEEP OUT OF REACH OF CHILDREN" in bold letters.
4. DIRECTION FOR USE:

   Special precautions regarding application of the product to certain fabrics should be included in the direction for use section of the label. See Appendix 1A, Section IV.

5. It appears that these formulations may pose a fire hazard. Based on the PCP Guidelines each registrant should determine whether their product needs a flammable sign, symbol and signal word on the label, based on the flash point and combustability of their product.

   Any Commercial classification, high concentration petroleum product requires: "Product contains Petroleum Distillate. Do not store, pour or use near open flame."

6. PRECAUTIONS:

   May be harmful if swallowed or absorbed through the skin, may cause skin and eye irritation. Do not get on skin, clothing or in eyes. Avoid breathing vapour. Wear impermeable gloves or goggles or face shield when handling. Wash hands thoroughly with soap and water after using product. Toxic to fish, plant life and animals. DO NOT STORE IN DWELLINGS.

7. FIRST AID:

   IF IN EYES, flush eyes with water for 5 minutes and get medical attention.

   IF ON SKIN, remove contaminated clothing and wash skin and hair immediately with soap and water. *Wash contaminated clothing separately from other laundry.*

   IF SWALLOWED, phone Poison Control Centre, hospital or doctor immediately.

8. TOXICOLOGICAL INFORMATION:

   Active ingredient is a metabolic stimulant and causes hyperthermia. Treat symptomatically. Chemical burns can result from eye contact or prolonged skin contact.

9. DISPOSAL:

   1. Rinse the emptied container thoroughly and add the rinsings to treatment site.
   2. Follow provincial instructions for any required additional cleaning of the container prior to its disposal or reconditioning.
   3. Dispose of the container in accordance with provincial requirements.
   4. For information on the disposal of unused, unwanted product and cleanup of spills contact the regional office the Environmental Protection Service, Environment Canada.
   5. For small spills. Recover free liquid. Soak up residue with solids absorbent. DO NOT FLUSH INTO SURFACE STREAMS. INFORM ENVIRONMENT CANADA AS IN # 4.

Group E:

All registrations of manufacturing purposes solids (SO, GP, SG) containing 85% pentachlorophenol, tetrachlorophenol, sodium pentachlorophenate, sodium tetrachlorophenate, and related chlorophenols or chlorophenates.

The following should appear on all Manufacturing (Group E) labels and applies to formulating from the solid technical material only.

Labelling for end product would depend on their formulation and use:

1. The DANGER POISON sign, symbol and signal words.
2. The words "READ LABEL BEFORE USING" in bold letters.
3. The words "KEEP OUT OF REACH OF CHILDREN" in bold letters.
4. PRECAUTIONS:

   Harmful or fatal if swallowed, inhaled or absorbed through the skin. Causes skin, eye and throat irritation. Do not get on skin, clothing or in eyes. Do not breath vapours or dust. Wear *impermeable* synthetic rubber gloves and eye goggles or face shield when handling concentrate. Wear a dust respirator and use only under well ventilated conditions. Wash thoroughly with soap and water after handling product. Toxic to fish, plant life and animals. Close container when not in use.
5. DIRECTIONS FOR USE:

   "NOT FOR USE IN DWELLINGS" and other limitations against use indoors should be stated on the label under the directions for use. See Appendix 1A, Section V for the appropriate directions for use and limitations.
6. FIRST AID:

   IF IN EYES, flush eyes with water for 5 minutes and get medical attention.

   IF ON SKIN, remove contaminated clothing and wash skin and hair with soap and water. Wash contaminated clothing before reuse, *separately from other laundry*.

   IF unformulated material is SWALLOWED, phone poison control centre, hospital or doctor immediately. Induce vomiting in conscious patient by tickling back of throat or using syrup of ipecac (15 mL). Repeat until vomit is clear.
7. TOXICOLOGICAL INFORMATION:

   Product is a metabolic stimulant and causes hyperthermia. Treat symptomatically. Chemical burns can result from eye contact or prolonged skin contact.
8. DECONTAMINATION AND DISPOSAL:

   Follow provincial instructions for any required additional cleaning of the container prior to its disposal or reconditioning.

   Dispose of the container in accordance with provincial requirements.

   For information on the disposal of unused, unwanted product and the cleanup of spills contact the regional office the Environmental Protection Service, Environment Canada.

   For small spills. Recover free liquid. Soak up residue with solids absorbent. DO NOT FLUSH INTO SURFACE STREAMS. INFORM ENVIRONMENT CANADA.

Group G

The registrations of solutions (SN) and pellets (PF) in the COMMERCIAL class (C) as cooling tower slimicide/algicides containing sodium pentachlorophenate, sodium tetrachlorophenate, other related chlorophenates or active ingredients.

The following should appear on all COMMERCIAL (Group G) labels:

1. Based on the pH of their formulation each registrant should place on the label and corrosive sign, symbol and signal word where necessary (see Appendix 1A).
2. The words "KEEP OUT OF REACH OF CHILDREN" in bold letters.
3. The words "READ LABEL BEFORE USING" in bold letters. NOT FOR USE IN DWELLINGS.
4. PRECAUTIONS:

   Harmful if swallowed, absorbed through the skin or inhaled. Causes skin and eye irritation. Avoid breathing vapour dust or spray. Wear synthetic rubber gloves and goggles or face shield when handling. Wash thoroughly with soap and water after use. Wash contaminated clothing *separately from other laundry*. Toxic to fish, plant life and animals. Close container when not in use.
5. FIRST AID:

   IF IN EYES, flush eyes with water for 5 minutes and get medical attention.

   IF ON SKIN, remove contaminated clothing and wash skin and hair immediately.

   IF SWALLOWED, phone poison control centre, hospital or physician immediately. Induce vomiting in conscious patient by gently tickling back of throat or by administering 15 mL syrup of ipecac. Repeat until vomit is clear.
6. TOXICOLOGICAL INFORMATION:

   Active ingredient is a metabolic stimulant and causes hyperthermia. Treat symptomatically. Chemical burns can result from eye contact or prolonged skin contact.
7. Limitations regarding use on materials coming into contact with potable water and environmental concerns should be placed under the Directions for Use. See Appendix 1A, Section IV for the appropriate direction for use limitations.
8. DISPOSAL:

   1. Rinse the emptied container thoroughly and add the rinsings to treatment site.

2. Follow provincial instructions for any required additional cleaning of the container prior to its disposal or reconditioning.
3. Dispose of the container in accordance with provincial requirements.
4. For information on the disposal of unused, unwanted product and cleanup of spills contact the regional office the Environmental Protection Service, Environment Canada.
5. For small spills. Recover free liquid. Soak up residue with solids absorbent. DO NOT FLUSH INTO SURFACE STREAMS. INFORM ENVIRONMENT CANADA AS IN # 4.

Group H1:

All registrations in the COMMERCIAL class (C) of solutions (SN) and suspensions (SU) used for sapstain control containing sodium pentachlorophenate, sodium tetrachlorophenate, and/or related chlorophenates and other active ingredients.

The following statements should be placed on all Group H1 labels:

1. Based on the pH of their product, each registrant should place on the label the appropriate poison sign, symbol and signal word and the appropriate corrosive sign, symbol and signal word, where necessary.
2. The words "READ LABEL BEFORE USING" "NOT FOR USE IN DWELLINGS" or "EXTERIOR USE ONLY" in bold letters.
3. The words "KEEP OUT OF REACH OF CHILDREN" in bold letters.
4. PRECAUTIONS:

   May be harmful or fatal if swallowed, inhaled or absorbed through the skin. Causes skin and eye irritation. Do not get on clothing, skin or in eyes. Wear impermeable clothing and footwear and impermeable synthetic rubber gloves when handling concentrate, spray solution or freshly treated wood. Wear eye goggles or face shield when handling concentrate or spray solution. Wear a chemical cartridge respirator with prefilter when mixing concentate, or when spray treating. Ensure adequate ventilation.

   Individuals who enter, clean, weld, or repair vats, tanks or other related equipment that is contaminated with the treatment solution must wear a respirator.

   Individuals must wear protective clothing (gloves, overalls, jackets, boots, head covering) impervious to the wood treatment formulation where dermal contact is expected.

   Individuals must not eat, drink or use tobacco products during those parts of the application process that may expose them to the wood treatment formulation.

   Wash thoroughly after skin contact and before eating, drinking, use of tobacco products or using restrooms.

   Protective clothing must be changed when it shows signs of contamination. Leave protective clothing at the plant. Launder work clothes separately from household items.

   DO NOT BURN chlorophenate treated wood in domestic stoves.

   This product is toxic to fish, wildlife and plant life.

   * For further information on the storage, handling, preparation, application and disposal of chlorophenate wood preservatives refer to Environment Canada and B.C. Ministry of Environment publication "Chlorophenate Wood Protection" (Konasewich *et al.*, 1983).

5. FIRST AID:

   IF IN EYES, flush eyes with water for 5 minutes and get medical attention.

   IF ON SKIN, remove contaminated clothing and wash skin and hair immediately with soap and water. Wash contaminated clothing before reuse, *separately from other laundry*.

   IF SWALLOWED, phone poison control centre, hospital or doctor immediately. Induce vomiting in conscious patient by gently tickling back of throat or by administering 15 mL syrup of ipecac. Repeat until vomit is clear.

6. TOXICOLOGICAL INFORMATION:

   Active ingredient is a metabolic stimulant and causes hyperthermia. Treat symptomatically. Chemical burns can result from eye contact or prolonged skin contact.

7. DIRECTIONS FOR USE:

   The appropriate rates of application use limitations and directions should be included for all products.

   See Appendix 1A, Sections VI and VII for the appropriate use limitations and precautions.

8. DISPOSAL:
   1. Rinse the emptied container thoroughly and add the rinsings to treatment site.
   2. Follow provincial instructions for any required additional cleaning of the container prior to its disposal or reconditioning.
   3. Dispose of the container in accordance with provincial requirements.
   4. For information on the disposal of unused, unwanted product and the cleanup of spills contact the regional office of the Environmental Protection Service, Environment Canada.
   5. For small spills. Recover free liquid. Soak up residue with solids absorbent. DO NOT FLUSH INTO SURFACE STREAMS. INFORM ENVIRONMENT CANADA AS IN # 4.

Group H2:

Registrations of COMMERCIAL class (C) soluble granule (SG) used for sapstain control, containing sodium pentachlorophenate, and other active ingredients.

1. Based on the pH of their product, each registrant should place on the label the appropriate corrosive sign, symbol and signal word, where necessary.
2. The words "READ LABEL BEFORE USING" in bold letters.
3. The words "KEEP OUT OF REACH OF CHILDREN" in bold letters.
4. PRECAUTIONS:

   May be harmful or fatal if swallowed, inhaled or absorbed through the skin. Causes skin and eye irritation. Do not get on clothing, skin or in eyes. Wear impermeable clothing and footwear and impermeable synthetic rubber gloves when handling concentrate, spray solution or freshly treated wood. Wear eye goggles or face shield when handling concentrate or spray solution. Wear a chemical cartridge respirator with prefilter when mixing concentrate, or when spray testing. Ensure adequate ventilation. Wash thoroughly with soap and water after use. Toxic to fish, plant life and animals.
5. FIRST AID:

   IF IN EYES, flush with water for 5 minutes and get medical attention.

   IF ON SKIN, remove contaminated clothing and wash skin and hair immediately with soap and water. Wash contaminated clothing before reuse, *separately from other laundry*.

   IF SWALLOWED, phone poison control centre, hospital or doctor immediately. Induce vomiting in conscious patient by gently tickling back of throat or by administering 30 mL syrup of ipecac.
6. TOXICOLOGICAL INFORMATION:

   Product is a metabolic stimulant and causes hyperthermia. Treat symptomatically. Chemical burns can result from eye contact or prolonged skin contact.
7. DIRECTIONS FOR USE:

   See Appendix 1A, Section VII for the appropriate directions for use limitations and appropriate environmental precautions.
8. DISPOSAL:
   1. Rinse the emptied container thoroughly and add the rinsings to treatment site.
   2. Follow provincial instructions for any required additional cleaning of the container prior to its disposal or reconditioning.
   3. Dispose of the container in accordance with provincial requirements.
   4. For information on the disposal of unused, unwanted product and the cleanup of spills contact the regional office of the Environmental Protection Service, Environment Canada.
   5. For small spills. Recover free liquid. Soak up residue with solids absorbent. DO NOT FLUSH INTO SURFACE STREAMS. INFORM ENVIRONMENT CANADA AS IN #4.

Appendix 1A, Section I
Use Limitations
Label Statements L.I.P. Program

I. Product Classification: COMMERCIAL

Wood preservatives containing pentachlorophenol in petroleum distillates.

II. Directions for Use

- o Do not apply this product to interior surfaces of domestic dwellings or farm buildings.
- o Do not apply to logs for construction of log homes.
- o This product is NOT to be used on children's playground equipment, horticultural lumber, including greenhouses, picnic tables or other food contact surfaces.
- o Do not apply this product where it may become a component of food, drinking water supplies, or animal feeds.
- o Do not burn treated wood.
- o Do not apply this product by spray methods.
- o Do not apply this product as an onsite treatment to water-front structures, such as docks, wharfs and rafts.
- o Do not apply this product as a soil sterilant or herbicide.

Appendix 1A, Section II
Use Limitations
Label Statements L.I.P. Program

I. Product Classification: DOMESTIC

Wood stains and wood preservatives containing pentachlorophenol in petroleum distillates.

II. Directions for Use

- o FOR EXTERIOR USE ONLY.
- o Apply by brush treatment.
- o Do not apply this product to interior surfaces of Domestic dwellings or farm buildings. Do not apply to logs for construction of log homes.
- o This product is NOT to be used on children's playground equipment, horticultural lumber, including greenhouses, picnic tables, or other food contact surfaces.

- o Do not apply this product where it may contact or contaminate drinking water supplies, food or animal feed.
- o Do not burn treated wood.
- o Do not apply this product by spray methods.
- o Do not apply this product as a soil steriiant or herbicide.
- o Do not apply this product as an onsite treatment to water-front structures, such as docks, wharfs and rafts.

Appendix 1A, Section III
Use Limitations
Label Statements L.I.P. Program

I. Product Classification: COMMERCIAL (Industrial)

Wood preservatives containing pentachlorophenol for use in remedial or groundline treatment of utility poles and railway ties.

II. Directions for Use

- o FOR EXTERIOR USE ONLY.
- o Do not apply this product to interior surfaces of domestic dwellings or farm buildings.
- o Do not apply to logs for construction of log homes.
- o This product is NOT to be used on children's playground equipment, horticultural lumber, including greenhouses, picnic tables, or other food contact surfaces.
- o Do not apply this product where it may become a component of food, drinking water supplies, or animal feed.
- o Do not burn treated wood.
- o Do not apply this product by spray methods.
- o Provide mechanical protection to above ground portions of the treatment formulation or of pole groundline bandages, where ever contact by persons, pets or farm animals may occur.

Appendix 1A, Section IV
Use Limitations
Label Statements L.I.P. Program

I. Product Classification: COMMERCIAL

(Category Materials Preservation)

Products for material preservation and water treatment which contain salts of pentachlorophenol or tetrachlorophenol.

Use areas include: paints, leather, adhesives, textiles, paper products, cordage, oil field floodwaters, packer fluids and mossicides.

II. Directions for Use

- o Do not incorporate into materials whose end use will result in prolonged skin contact e.g. life jackets, sleeping bags, sports equipment.
- o Products treated with or containing this chemical are not to be used in food packaging materials or in areas where food is processed, handled or stored.
- o Do not use in the pretanning operations of curing, liming, soaking and pickling from which by-product fats result.
- o Do not use this product in the production of paper or paperboard that comes in contact with food, or growing plants.
- o Do not use as a pulp and paper slimicide.
- o For use in closed or recirculating water cooling systems only.
- o Do not reuse or collect water from roofs on which this product has been applied as a mossicide.
- o Do not apply this product as a soil sterilant or herbicide.
- o Do not apply chlorophenols to oil well flood waters or packer fluids in offshore locations.

Appendix 1A, Section V
Use Limitations
Label Statements L.I.P. Program

I. Product Classification: Commercial or Manufacturing

Pentachlorophenol and tetrachlorophenol for use in the manufacture of wood preservatives registered under the P.C.P. Act and for use in pressure treating facilities.

II. Directions for Use

- o FOR EXTERIOR USE ONLY.
- o Do not apply to logs used in the construction of log homes.
- o Do not use pentachlorophenol treated wood in residential interiors or interiors of farm buildings.
- o Do not apply pentachlorophenol to wood intended for farrowing or brooding facilities or where domestic animals or livestock are likely to crib or lick the wood.
- o Do not apply to products where the preservative may contact or become a component of food or animal feed.
- o Do not apply to products where the preservative may come into direct or indirect contact with drinking water.
- o Do not apply to products where prolonged skin contact with the treated material is likely to occur.
- o Do not apply to greenhouse or horticultural lumber.
- o Do not apply to children's playground equipment.

- o Do not use pentachlorophenol in food packaging materials or in areas where food is processed, handled, stored or transported.
- o For powdered, prilled, flake, or glazed forms use closed mixing systems when formulating products or treating solutions.
- o Individuals who mix formulations, clean, enter, repair or weld equipment contaminated with chlorophenol deposits or treatment formulation must wear a respirator and protective clothing impervious to the treatment formulation (head gear, jacket, pants, boots).
- o Individuals must wear a respirator and protective clothing impervious to the formulation when opening cylinder doors at pressure treating facilities.
- o Individuals exposed to vapors from charges of treated wood which are above ambient temperature must wear a respirator and protective clothing impervious to the formulation.
- o Wear protective clothing impervious to the formulation when dermal contact is expected (gloves, jacket, pants, boots).
- o Individuals must not eat, drink or use tobacco products during those parts of the process that may expose them to the wood treatment formulation.
- o Wash thoroughly after skin contact and before eating, drinking, use of tobacco products or using restrooms.
- o Protective clothing must be changed when it shows signs of contamination. Leave all protective clothing at the plant. Launder work clothing separately from other household items.
- o DO NOT BURN OR BRAND pentachlorophenol treated wood.

* For further detailed information on the storage, handling, preparation, application and disposal of chlorophenol wood preservatives, refer to Environment Canada publication "Recommendations for the Design and Operation of Pentachlorophenol Pressure Treating Wood Preserving Facilities".

Appendix 1A, Section VI
Use Limitations
Label Statements (Pentachlorophenol)

I. Product Classification: COMMERCIAL

Commercial wood preservatives for use in treatment of window sash, *exterior* millwork and *exterior* joinery items.

II. Directions for Use

Commercial spray box, flow coating or dip tank equipment must be free of leaks with provision to eliminate or contain, mist, overspray, drips, and spillage into the surrounding environment.

- o Freshly treated wood must be dried in an area with adequate ventilation to remove vapours and to contain residual deposits or drips of the formulation.
- o Do not apply to logs used in the construction of log homes.
- o Operators and individuals who enter, clean, repair or weld vats, tanks or other related equipment contaminated with the treatment solution must wear a respirator.
- o Where dermal contact is expected, individuals must wear protective clothing (jacket, pants (or an apron), gloves and boots) impervious to the treatment formulation.
- o Applicators must not eat, drink or use tobacco products during those parts of the application process that may expose them to the wood treatment formulation or concentrates.
- o Protective clothing must be changed when it shows signs of contamination. Leave all protective clothing at the plant.
- o For disposal of high-level contaminated wastes (debris, bottom sludge, filter wastes), unused, unwanted product and the cleanup of spills contact the regional office of the Environmental Protection Service, Environment Canada.

Appendix 1A, Section VII
Use Limitations
Label Statements

I. Product Classification: Commercial

For all products labelled as wood preservatives for sapstain control and containing salts of pentachlorophenol/ tetrachlorophenol the following language must appear on the labels:

II. Directions for Use

- o For use only in commercial spray box, flow coating or dip tanks. Equipment must be free of leaks with provision to eliminate or contain mist, overspray, drips, and spillage into the surrounding environment.
- o Dip tanks and storage areas for freshly dipped lumber should not be located adjacent to water bodies. Dip tanks should be covered. Allow lumber to "drip dry" on the apron of the dip tank before it is removed to storage areas.
- o Freshly treated wood should be protected from rainfall until formulation has fixed.
- o Do not apply this product by back pack or portable spray equipment.
- o For powdered, prilled, or flake formulations use closed mixing systems only.
- o Do not use shavings from chlorophenate treated lumber for animal bedding or poultry litter.

Appendix 2.

Overview of Health-based Guidelines from the Codes of Good Practice in the Wood Preservation and Wood Protection Industries.

The Codes of Good Practice present voluntary guidelines for the design and operation of wood preservation and protection facilities (Konasewich *et al.*, 1983; Konasewich and Henning, 1987). These recommendations are designed to reduce industrial exposure to and environmental contamination from PCP, T_4CP and their sodium salts at such facilities. Readers requiring the specific guidelines are referred to the above reports. In general terms, the health-based guidelines include recommendations to:

1. Train workers in the safe handling and transport of these chemicals and in the operation and maintenance of the wood treatment facility, and periodic review of these procedures with workers.
2. Ensure workers access to and training with appropriate first-aid equipment, and periodic review of these procedures with workers.
3. Provide workers who contact lumber or contaminated equipment with impermeable gloves (Silkowski *et al.*, 1984) and aprons and coveralls if their tasks require them; employees in all working areas should wear impermeable footwear.
4. Use eye or face protection if contact of chlorophenols with these areas is possible.
5. Practice careful personal hygiene, including: employee washing-up prior to eating, smoking or work breaks; showers post-shift; laundering of work clothing between daily uses, separately from other clothing.
6. Rotate employees between tasks which involve high-level exposure to chlorophenols and those which are characterized by lesser exposures.
7. Conduct pre-employment and annual ongoing medical surveillance of employees.
8. Use closed systems (with appropriate provisions for equipment monitoring and failure) for spraying, dipping or pressure treatment of wood, and where chlorophenols are mixed and stored. In this context, drive-through tanks should be eliminated for antisapstain treatment, in consideration of the inability to isolate workers from exposure to chlorophenates.
9. Use a roofed facility, designed to contain spillage or leachate, for the mixing of chlorophenol solutions, the storage of lumber while antisapstain chemicals are 'fixing' to wood, or the storage of most contaminated wastes.
10. Pay careful attention to facility housekeeping practices, including: the labelling of storage areas and tanks to identify contents and appropriate emergency procedures; containment of contaminated debris; washing down of the floor or pavement in handling areas; rinsing of empty containers; the recycling of rinse water; a periodic thorough cleaning of the treatment apparatus; additional precautions when washing contaminated equipment; site monitoring.

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